



Clinical trial results:

A double blind, randomized placebo controlled crossover multiple dose study of LJN452 to assess safety, tolerability and efficacy in patients with primary bile acid diarrhea (pBAD)

Summary

EudraCT number	2015-003192-30
Trial protocol	GB
Global end of trial date	25 January 2018

Results information

Result version number	v1 (current)
This version publication date	10 February 2019
First version publication date	10 February 2019

Trial information

Trial identification

Sponsor protocol code	CLJN452X2202
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02713243
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 January 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	25 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the safety and tolerability of LJN452 in patients with primary bile acid diarrhea.
To assess the effect of LJN452 on clinical symptoms experienced by patients with primary bile acid diarrhea.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 April 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	United States: 8
Worldwide total number of subjects	20
EEA total number of subjects	12

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	15
From 65 to 84 years	5

85 years and over	0
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Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

In total, 20 patients were enrolled in this study and received at least one dose of LJN452 or matching placebo for 14 days in Period 1. There will be a washout period between 7 to 28 days followed by Period 2 drug if patient on LJN452 or Placebo in Period 1 they will take Placebo or LJN452 respectively in Period 2 for 14 days

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	LJN452 followed by placebo

Arm description:

Randomized patients in this arm will receive single oral dose of LJN452 daily for 14 days. There will be a washout period between 7 to 28 days followed by single oral dose of placebo daily for 14 days.

Arm type	Experimental
Investigational medicinal product name	Placebo to match LJN452
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo to match LJN453 daily for 14 days

Investigational medicinal product name	Tropifexor
Investigational medicinal product code	LJN452
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

LJN453 60 mcg daily for 14 days

Arm title	Placebo followed by LJN452
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Arm description:

Randomized patients in this arm will receive single oral dose of placebo daily for 14 days. There will be a washout period between 7 to 28 days followed by single oral dose of LJN452 daily for 14 days.

Arm type	Placebo
Investigational medicinal product name	Tropifexor
Investigational medicinal product code	LJN452
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

LJN453 60 mcg daily for 14 days

Investigational medicinal product name	Placebo to match LNJ452
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo to match LNJ453 daily for 14 days

Number of subjects in period 1	LNJ452 followed by placebo	Placebo followed by LNJ452
Started	10	10
Completed	9	8
Not completed	1	2
Abnormal laboratory value(s)#	1	-
Protocol deviation	-	1
Administrative problems	-	1

Baseline characteristics

Reporting groups

Reporting group title	LJN452 followed by placebo
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Reporting group description:

Randomized patients in this arm will receive single oral dose of LJN452 daily for 14 days. There will be a washout period between 7 to 28 days followed by single oral dose of placebo daily for 14 days.

Reporting group title	Placebo followed by LJN452
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Reporting group description:

Randomized patients in this arm will receive single oral dose of placebo daily for 14 days. There will be a washout period between 7 to 28 days followed by single oral dose of LJN452 daily for 14 days.

Reporting group values	LJN452 followed by placebo	Placebo followed by LJN452	Total
Number of subjects	10	10	20
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	9	6	15
From 65-84 years	1	4	5
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	49.4	57.9	
standard deviation	± 13.25	± 16.47	-
Sex: Female, Male Units: Subjects			
Female	4	8	12
Male	6	2	8
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	10	10	20
More than one race	0	0	0
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	LJN452 followed by placebo
Reporting group description: Randomized patients in this arm will receive single oral dose of LJN452 daily for 14 days. There will be a washout period between 7 to 28 days followed by single oral dose of placebo daily for 14 days.	
Reporting group title	Placebo followed by LJN452
Reporting group description: Randomized patients in this arm will receive single oral dose of placebo daily for 14 days. There will be a washout period between 7 to 28 days followed by single oral dose of LJN452 daily for 14 days.	
Subject analysis set title	LJN452 ALL Patients
Subject analysis set type	Per protocol
Subject analysis set description: All Patients on LJN452 in both Period 1 and Period 2	
Subject analysis set title	Placebo ALL Patients
Subject analysis set type	Per protocol
Subject analysis set description: All Patients on Placebo in both Period 1 and Period 2	
Subject analysis set title	LJN452 ALL Patients
Subject analysis set type	Sub-group analysis
Subject analysis set description: All Patients on LJN452 in both Period 1 and Period 2	

Primary: Number of patients reported with adverse events , serious adverse events and death.

End point title	Number of patients reported with adverse events , serious adverse events and death. ^[1]
End point description: Number of patients reported with adverse events , serious adverse events and death. Adverse events were summarized using descriptive statistics only with no formal statistical analysis performed.	
End point type	Primary
End point timeframe: up to Day 79	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Adverse events were summarized using descriptive statistics only with no formal statistical analysis performed.

End point values	LJN452 ALL Patients	Placebo ALL Patients		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: count of participants				
AEs, Patients with AEs	9	14		
Study drug-related AEs	0	4		
Serious AEs	0	0		
Death	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Stool frequency at Baseline, Week 1 (Period 1 & Period 2), Week 2 (Period 1 & Period 2), and Week 1 & 2 combined

End point title	Stool frequency at Baseline, Week 1 (Period 1 & Period 2), Week 2 (Period 1 & Period 2), and Week 1 & 2 combined
End point description:	Stool frequency at Baseline, Week 1 (Period 1 & Period 2), Week 2 (Period 1 & Period 2), and Week 1 & 2 combined
End point type	Primary
End point timeframe:	Baseline, Week 1 (Period 1 & Period 2), Week 2 (Period 1 & Period 2), and Week 1 & 2 combined

End point values	LJN452 ALL Patients	Placebo ALL Patients		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: stool frequency				
arithmetic mean (standard deviation)				
Baseline	18.0 (± 9.39)	15.9 (± 6.92)		
Week 1 (Period 1 & 2)	20.0 (± 11.62)	16.2 (± 7.19)		
Week 2 (Period 1 & 2)	18.8 (± 9.68)	17.5 (± 10.88)		
Week 1 & 2(Period 1 & 2)	19.4 (± 10.56)	16.8 (± 9.11)		

Statistical analyses

Statistical analysis title	Stool Frequency Week 1 (Period 1 & 2)
Statistical analysis description:	Week 1 (Period 1 & 2) -Due to EudraCT system limitations, which EMA is aware of, results of crossover studies are not accurately represented in this record. Please go to https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.
Comparison groups	LJN452 ALL Patients v Placebo ALL Patients
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Mixed models analysis
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	7.11

Statistical analysis title	Stool Frequency Week 1&2 (Period 1 & 2)
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Statistical analysis description:

Week 1&2 (Period 1 & 2) Due to EudraCT system limitations, which EMA is aware of, results of crossover studies are not accurately represented in this record. Please go to <https://www.novctrd.com/CtrdWeb/home.nov> for complete trial results.

Comparison groups	LJN452 ALL Patients v Placebo ALL Patients
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.019
Method	Mixed models analysis
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	4.89

Statistical analysis title

Stool Frequency Week 2 (Period 1 & 2)

Statistical analysis description:

Week 2 (Period 1 & 2) Due to EudraCT system limitations, which EMA is aware of, results of crossover studies are not accurately represented in this record. Please go to <https://www.novctrd.com/CtrdWeb/home.nov> for complete trial results.

Comparison groups	LJN452 ALL Patients v Placebo ALL Patients
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.401
Method	Mixed models analysis
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.77
upper limit	4.38

Primary: Stool form at Baseline, Week 1 (Period 1 & Period 2), Week 2 (Period 1 & Period 2), and Week 1 & 2 combined

End point title	Stool form at Baseline, Week 1 (Period 1 & Period 2), Week 2 (Period 1 & Period 2), and Week 1 & 2 combined
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End point description:

Stool Form at Baseline, Week 1 (Period 1 & Period 2), Week 2 (Period 1 & Period 2), and Week 1 & 2 combined Clinical Symptoms will be measured as change from baseline in stool types per Bristol Stool Scale. The Bristol Stool Scale is a medical aid designed to classify feces on a scale from 1 to 7 according to increasing wateriness.

End point type	Primary
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End point timeframe:

Baseline, Week 1 (Period 1 & Period 2), Week 2 (Period 1 & Period 2), and Week 1 & 2 combined

End point values	LJN452 ALL Patients	Placebo ALL Patients		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline	5.5 (± 0.87)	5.1 (± 0.94)		
Week 1 (Period 1 & 2)	5.3 (± 0.78)	5.3 (± 0.79)		
Week 2 (Period 1 & 2)	4.9 (± 0.82)	5.1 (± 1.01)		
Week 1 & 2(Period 1 & 2)	5.1 (± 0.81)	5.2 (± 0.90)		

Statistical analyses

Statistical analysis title	Stool Form Week 1 (Period 1 & 2)
Statistical analysis description:	
Week 1 (Period 1 & 2) Due to EudraCT system limitations, which EMA is aware of, results of crossover studies are not accurately represented in this record. Please go to https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.	
Comparison groups	LJN452 ALL Patients v Placebo ALL Patients
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.533
Method	Mixed models analysis
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	0.52

Statistical analysis title	Stool Form Week 1&2 (Period 1 & 2)
Statistical analysis description:	
Week 1&2 (Period 1 & 2) Due to EudraCT system limitations, which EMA is aware of, results of crossover studies are not accurately represented in this record. Please go to https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.	
Comparison groups	LJN452 ALL Patients v Placebo ALL Patients
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.916
Method	Mixed models analysis
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	0.3

Statistical analysis title	Stool Form Week 2 (Period 1 & 2)
Statistical analysis description: Week 2 (Period 1 & 2) Due to EudraCT system limitations, which EMA is aware of, results of crossover studies are not accurately represented in this record. Please go to https://www.novctrd.com/CtrdWeb/home.nov for complete trial results.	
Comparison groups	LJN452 ALL Patients v Placebo ALL Patients
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.64
Method	Mixed models analysis
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.49
upper limit	0.3

Secondary: Area under the plasma concentration-time profile (AUCtau) of LJN452

End point title	Area under the plasma concentration-time profile (AUCtau) of LJN452
End point description: AUCtau- is the area under the plasma (or serum or blood) concentration-time curve from time zero to the end of the dosing interval tau [mass x time / volume]	
End point type	Secondary
End point timeframe: Day 1 (Period 1 & 2) and Day 12 (Period 1 & 2)	

End point values	LJN452 ALL Patients			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: hr*ng/mL				
arithmetic mean (standard deviation)				
Day 1	23.6 (± 7.24)			
Day 12	22.1 (± 4.83)			

Statistical analyses

No statistical analyses for this end point

Secondary: (Cmax) of LJN452

End point title	(Cmax) of LJN452
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End point description:

C_{max} is the observed maximum plasma (or serum or blood) concentration following drug administration [mass / volume]

End point type	Secondary
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End point timeframe:

Day 1 (Period 1 & 2) and Day 12 (Period 1 & 2)

End point values	LJN452 ALL Patients			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1	1.63 (± 0.414)			
Day 12	1.82 (± 0.704)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to reach maximum concentration after drug administration (T_{max})

End point title	Time to reach maximum concentration after drug administration (T _{max})
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End point description:

T_{max} is the time to reach the maximum concentration after drug administration [time]

End point type	Secondary
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End point timeframe:

Day 1 (Period 1 & 2) and Day 12 (Period 1 & 2)

End point values	LJN452 ALL Patients			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: hr				
median (full range (min-max))				
Day 1	5.00 (3.92 to 8.00)			
Day 12	5.00 (1.83 to 8.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total Dose of Rescue Medication used at Baseline, Week 1 (Period 1 & Period 2), Week 2 (Period 1 & Period 2), and Week 1 & 2 combined

End point title	Total Dose of Rescue Medication used at Baseline, Week 1 (Period 1 & Period 2), Week 2 (Period 1 & Period 2), and Week 1 & 2 combined
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End point description:

Total Dose of Rescue Medication used at Baseline, Week 1 (Period 1 & Period 2), Week 2 (Period 1 & Period 2), and Week 1 & 2 combined; Rescue Medication used was loperamide

End point type	Secondary
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End point timeframe:

Baseline, Week 1 (Period 1 & 2), Week 2 (Period 1 & 2), Week 1 & 2 combined

End point values	LJN452 ALL Patients	Placebo ALL Patients		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: mg				
arithmetic mean (standard deviation)				
Baseline	0.9 (± 3.50)	1.3 (± 5.66)		
Week 1 (Period 1 & 2)	0.6 (± 1.75)	0.7 (± 2.06)		
Week 2 (Period 1 & 2)	0.5 (± 1.37)	0.7 (± 1.68)		
Week 1 & 2(Period 1 & 2)	0.6 (± 1.54)	0.7 (± 1.85)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Placebo
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Reporting group description:

Placebo

Reporting group title	LJN452 60 ug
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Reporting group description:

LJN452 60 ug

Serious adverse events	Placebo	LJN452 60 ug	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 19 (0.00%)	0 / 17 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Placebo	LJN452 60 ug	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 19 (73.68%)	9 / 17 (52.94%)	
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	0 / 19 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Limb injury			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			

Dizziness			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Dysgeusia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Migraine			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	4 / 19 (21.05%)	2 / 17 (11.76%)	
occurrences (all)	4	2	
Tremor			
subjects affected / exposed	0 / 19 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 19 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Abdominal distension			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
subjects affected / exposed	1 / 19 (5.26%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Anal incontinence			
subjects affected / exposed	0 / 19 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Bile acid malabsorption			

subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 2	0 / 17 (0.00%) 0	
Constipation subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 17 (0.00%) 0	
Frequent bowel movements subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 17 (5.88%) 1	
Nausea subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 17 (0.00%) 0	
Hepatobiliary disorders Biliary dyspepsia subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 17 (0.00%) 0	
Skin and subcutaneous tissue disorders Dermatitis contact subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 17 (5.88%) 1	
Pruritus subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 17 (0.00%) 0	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 17 (5.88%) 1	
Musculoskeletal and connective tissue disorders Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 17 (5.88%) 1	
Myalgia subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 17 (5.88%) 1	
Infections and infestations Nasopharyngitis			

subjects affected / exposed	0 / 19 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	1 / 19 (5.26%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Upper respiratory tract infection			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 November 2015	Amendment 1: The purpose of this amendment was to address comments from the US FDA prior to start of the study. Specific limits for ALP and GGT were added that equate to the CTCAE grades within individual and stopping criteria.
15 August 2016	Amendment 2: The purpose of this amendment was to include new data from the embryo fetal developmental toxicity program. As a result of these new data, women of child bearing potential were allowed to participate in the study provided they utilized highly effective contraception. Changes were made to the inclusion criteria and to the assessment table with respect to optional pharmacokinetic and biomarker assessments to reduce patient burden.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, results of crossover studies are not accurately represented in this record. Please go to <https://www.novctrd.com/CtrdWeb/home.nov> for complete trial results.

Notes: