



## Clinical trial results:

### A Phase II, Dose Ranging, Exploratory Clinical Study to Assess the Efficacy, Pharmacodynamics, and Safety of LNP1955 in Patients with Moderate-to-Severe Plaque Psoriasis

#### Summary

EudraCT number	2016-001531-12
Trial protocol	HU
Global end of trial date	11 October 2017

#### Results information

Result version number	v1 (current)
This version publication date	08 March 2019
First version publication date	08 March 2019

#### Trial information

##### Trial identification

Sponsor protocol code	LRP/LNP1955/2016/003
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##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	Lupin Limited
Sponsor organisation address	46A/47A, Nande, Pune, India, 412115
Public contact	Project Director, Lupin Limited, 0091 20 66749068, chiragshah@lupin.com
Scientific contact	Project Director, Lupin Limited, 0091 20 66749068, chiragshah@lupin.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	11 October 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 October 2017
Global end of trial reached?	Yes
Global end of trial date	11 October 2017
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

The primary objectives of the study are as follows:

- To assess the POE of LNP1955 and find an optimum dose in patients with moderate-to-severe plaque psoriasis

Protection of trial subjects:

To alleviate the symptoms of Psoriasis, patients were allowed to use topical emollients, moisturizers, and shampoos without anti-psoriatic ingredients during the study period, antihistamines were also allowed as per investigators' discretion. In combination arm, along with methotrexate therapy, folic acid was allowed to be administered to avoid folate deficiency.

Based on review of ongoing safety monitoring of this study of LNP1955 conducted in Psoriasis (N=35 patients) in Europe, a significant number of patients reported elevations in AST/ALT; unblinding was done for these patients and it was observed that all patients belonged to active treatment arms, thus indicating an unfavorable risk: benefit ratio.

Such a potential risk for liver enzyme elevation is undesirable in a non-life-threatening condition such as psoriasis, which was one of the target indications for LNP1955.

In light of this cumulative assessment and keeping patient safety in mind, Sponsor decided to terminate this study of LNP1955 with due conscientiousness towards scientific rigor & commitment towards developing safe and effective research products.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 September 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Hungary: 35
Worldwide total number of subjects	35
EEA total number of subjects	35

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)	31
From 65 to 84 years	4
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

A total of 48 patients were screened for the study out of which 13 patients were screen failures and of these patients 35 were randomized/ enrolled in the main and Add on part of the study. Among those, 27 patients were randomized in Main double blind part and 8 patients on MTX add on part of the study.

### Pre-assignment

Screening details:

Male/female ambulatory patients aged 18 to 75 years diagnosed with moderate to severe chronic stable plaque psoriasis with active disease for at least 6 months, with a PASI score of  $\geq 10$  & affected body surface area (BSA)  $\geq 10\%$  and who were candidates for phototherapy, photo-chemotherapy, or systemic therapy for plaque Psoriasis

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	LNP1955 40 mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	LNP1955
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Enteral use

Dosage and administration details:

LNP1955 was administered orally two times a day for 12 weeks.

<b>Arm title</b>	LNP1955 80mg
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	LNP1955
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Enteral use

Dosage and administration details:

LNP1955 was administered orally two times a day for 12 weeks.

<b>Arm title</b>	Placebo
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	Placebo of LNP1955
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Enteral use

Dosage and administration details:

Placebo of LNP1955 was administered orally two times a day for 12 weeks.

<b>Arm title</b>	LNP1955 40mg +MTX
Arm description: This arm was an open label MTX add on part.	
Arm type	Experimental
Investigational medicinal product name	LNP1955
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Enteral use

Dosage and administration details:

LNP1955 40mg was administered orally two times a day for 12 weeks.

Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Enteral use

Dosage and administration details:

In the non-randomized, open label MTX Add on part of the study, patients received LNP1955 40 mg bid in combination with a fixed weekly dose of 7.5 mg of MTX administered orally in 3 divided doses of 2.5 mg approximately 12 hours apart.

<b>Number of subjects in period 1</b>	LNP1955 40 mg	LNP1955 80mg	Placebo
Started	10	9	8
Completed	4	6	7
Not completed	6	3	1
Physician decision	2	-	-
Adverse event, non-fatal	-	1	-
Sponsor decision	4	2	1

<b>Number of subjects in period 1</b>	LNP1955 40mg +MTX
Started	8
Completed	8
Not completed	0
Physician decision	-
Adverse event, non-fatal	-
Sponsor decision	-



## Baseline characteristics

### Reporting groups

Reporting group title	LNP1955 40 mg
Reporting group description: -	
Reporting group title	LNP1955 80mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	LNP1955 40mg +MTX
Reporting group description:	
This arm was an open label MTX add on part.	

Reporting group values	LNP1955 40 mg	LNP1955 80mg	Placebo
Number of subjects	10	9	8
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	40.9	39.8	45.3
standard deviation	± 14.66	± 11.44	± 18.20
Gender categorical Units: Subjects			
Female	2	2	1
Male	8	7	7

Reporting group values	LNP1955 40mg +MTX	Total	
Number of subjects	8	35	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years)		0 0 0 0 0 0 0	

From 65-84 years		0	
85 years and over		0	

Age continuous			
Units: years			
arithmetic mean	46.1		
standard deviation	± 12.83	-	
Gender categorical			
Units: Subjects			
Female	1	6	
Male	7	29	

## End points

### End points reporting groups

Reporting group title	LNP1955 40 mg
Reporting group description: -	
Reporting group title	LNP1955 80mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	LNP1955 40mg +MTX
Reporting group description: This arm was an open label MTX add on part.	
Subject analysis set title	LNP1955 40mg
Subject analysis set type	Safety analysis
Subject analysis set description: Safety population includes patients who are randomized and received at least one dose of IP. Patients will be analyzed based on the treatment they actually received.	
Subject analysis set title	LNP1955 80mg
Subject analysis set type	Safety analysis
Subject analysis set description: Safety population includes patients who are randomized and received at least one dose of IP. Patients will be analyzed based on the treatment they actually received.	
Subject analysis set title	Placebo
Subject analysis set type	Safety analysis
Subject analysis set description: Safety population includes patients who are randomized and received at least one dose of IP. Patients will be analyzed based on the treatment they actually received.	
Subject analysis set title	MTX add on arm
Subject analysis set type	Safety analysis
Subject analysis set description: Safety population includes patients who are randomized and received at least one dose of IP. Patients will be analyzed based on the treatment they actually received.	

### **Primary: • The proportion of patients achieving at least 75% reduction (PASI 75) from baseline in PASI after 12 weeks of treatment.**

End point title	• The proportion of patients achieving at least 75% reduction (PASI 75) from baseline in PASI after 12 weeks of treatment. <sup>[1]</sup>
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End point description:

End point type	Primary
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End point timeframe:

PASI score was assessed at each visit every 4 weeks until 12 weeks of treatment period.

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: Based on ongoing safety monitoring of study a significant number of patients reported elevations in AST/ALT in active treatment arms, thus indicating an unfavorable risk: benefit ratio. Such a potential risk for liver enzyme elevation is undesirable. In light of this cumulative assessment and keeping patient safety in mind, Sponsor decided to prematurely terminate the study and hence efficacy analysis (primary and secondary), PK-PD analysis was not performed.

End point values	LNP1955 40 mg	LNP1955 80mg	Placebo	LNP1955 40mg +MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 <sup>[2]</sup>	0 <sup>[3]</sup>	0 <sup>[4]</sup>	0 <sup>[5]</sup>
Units: NA				

Notes:

[2] - No Efficacy analysis done for this study

[3] - No Efficacy analysis done for this study

[4] - No Efficacy analysis done for this study

[5] - No Efficacy analysis done for this study

## Statistical analyses

No statistical analyses for this end point

## Secondary: Adevrse event assessment

End point title	Adevrse event assessment
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End point description:

End point type	Secondary
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End point timeframe:

Adverse event assessment is done at each visit until end of 12 weeks of treatment period and at follow up visit at 7 days after the end of treatment

End point values	LNP1955 40 mg	LNP1955 80mg	Placebo	LNP1955 40mg +MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	9	8	8
Units: NA	5	5	3	3

End point values	LNP1955 40mg	LNP1955 80mg	Placebo	MTX add on arm
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	9	8	8
Units: NA	5	5	3	3

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All AEs, regardless of severity, causality and whether or not they occur during the screening and washout period, treatment period of 12 weeks or FU period until 7 days after end of treatment,

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.1
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### Reporting groups

Reporting group title	LNP1955 40 mg
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Reporting group description: -

Reporting group title	LNP1955 80mg
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Reporting group title	LNP1955 40mg +MTX
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Reporting group description:

This arm was an open label MTX add on part.

Serious adverse events	LNP1955 40 mg	LNP1955 80mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Drug use disorder			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	LNP1955 40mg +MTX		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)		

number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Drug use disorder			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

<b>Non-serious adverse events</b>	LNP1955 40 mg	LNP1955 80mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 10 (50.00%)	5 / 9 (55.56%)	2 / 8 (25.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin Papilloma			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal Pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 10 (10.00%)	2 / 9 (22.22%)	0 / 8 (0.00%)
occurrences (all)	1	2	0
Aspartate Aminotransferase Increased			

subjects affected / exposed	0 / 10 (0.00%)	2 / 9 (22.22%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Hepatic Enzyme Increased			
subjects affected / exposed	0 / 10 (0.00%)	2 / 9 (22.22%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Blood Pressure Increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Electrocardiogram Qt Prolonged			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Haematocrit Decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Lipids Increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 10 (10.00%)	2 / 9 (22.22%)	0 / 8 (0.00%)
occurrences (all)	3	2	0
faeces soft			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Glossodynia			

subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 9 (11.11%) 1	0 / 8 (0.00%) 0
Hepatobiliary disorders Hepatic Cyst subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0	0 / 8 (0.00%) 0
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 9 (11.11%) 1	0 / 8 (0.00%) 0
Psoriasis subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0	0 / 8 (0.00%) 0
Seborrhea subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 9 (11.11%) 1	0 / 8 (0.00%) 0
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 9 (11.11%) 1	0 / 8 (0.00%) 0
Renal Cyst subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0	0 / 8 (0.00%) 0
Musculoskeletal and connective tissue disorders Back Pain subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 9 (11.11%) 1	0 / 8 (0.00%) 0
Infections and infestations Erysipelas subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 2	0 / 9 (0.00%) 0	0 / 8 (0.00%) 0
Fungal Infection subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 9 (0.00%) 0	0 / 8 (0.00%) 0
Oral Herpes			

subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	2	0	0
Pyuria			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Herpes Simplex			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Cholesterosis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 9 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0

<b>Non-serious adverse events</b>	LNP1955 40mg +MTX		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 8 (37.50%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin Papilloma			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal Pain			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Aspartate Aminotransferase Increased			

subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Hepatic Enzyme Increased			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Blood Pressure Increased			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Electrocardiogram Qt Prolonged			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Gamma-Glutamyltransferase Increased			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Haematocrit Decreased			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Lipids Increased			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
faeces soft			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Glossodynia			

subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Hepatobiliary disorders Hepatic Cyst subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all)  Psoriasis subjects affected / exposed occurrences (all)  Seborrhea subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0  0 / 8 (0.00%) 0  0 / 8 (0.00%) 0		
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)  Renal Cyst subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0  0 / 8 (0.00%) 0		
Musculoskeletal and connective tissue disorders Back Pain subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Infections and infestations Erysipelas subjects affected / exposed occurrences (all)  Fungal Infection subjects affected / exposed occurrences (all)  Oral Herpes	0 / 8 (0.00%) 0  0 / 8 (0.00%) 0		

subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Pyuria			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Herpes Simplex			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Cholesterosis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### 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.

Based on ongoing safety monitoring significant number of patients reported elevations in AST/ALT in active treatments arms hence, study was terminated prematurely in view of patient's safety. Efficacy, PK, PD were thus not analyzed for this study.
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Notes: