Clinical trial results:
A 12-week randomized, patient and investigator blinded, placebo-controlled, parallel group study to investigate the efficacy of LIK066 in obese patients with NASH.

Summary

EudraCT number	2017-002046-71
Trial protocol	NL
Global end of trial date	14 November 2019

Results information

Result version number	v1 (current)
This version publication date	27 November 2020
First version publication date	27 November 2020

Trial information

Trial identification

Sponsor protocol code	CLIK066X2204

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03205150
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	14 November 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to determine the effect of LIK066 on liver function test (circulating ALT) after 12 weeks of treatment.

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:

All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, were recorded on the Concomitant medications/Significant non-drug therapies CRF.

Evidence for comparator: -

Actual start date of recruitment	04 October 2017
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	Argentina: 23
Country: Number of subjects enrolled	Canada: 18
Country: Number of subjects enrolled	Israel: 11
Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	Russian Federation: 9
Country: Number of subjects enrolled	Taiwan: 9
Country: Number of subjects enrolled	Thailand: 3
Country: Number of subjects enrolled	United States: 27
Worldwide total number of subjects	107
EEA total number of subjects	7

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)	95
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 107 participants were enrolled in 15 centers across 8 countries: Argentina (2), Canada (1), Israel (3), Netherlands (1), Russia federation (1), Taiwan (2), Thailand (1), United States (4).

Pre-assignment

Screening details:

Participants were randomized in 2:2:1 ratio to the 3 groups: LIK066 150 mg, LIK066 30 mg and placebo.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	LIK066 30 mg

Arm description:

Film coated tablet of LIK066 30 mg was mostly administered once daily before lunch, except on Day 56 when it was administered before breakfast and in fasted state on Day 84.

Arm type	Experimental
Investigational medicinal product name	LIK066
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

once daily oral dose of LIK066 30 mg

Arm title	LIK066 150 mg

Arm description:

Film coated tablet of LIK066 150 mg was mostly administered once daily before lunch, except on Day 56 when it was administered before breakfast and in fasted state on Day 84.

Arm type	Experimental
Investigational medicinal product name	LIK066
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

once daily oral dose of LIK066 150 mg

Arm title	Placebo

Arm description:

LIK066 0 mg film-coated tablet(Placebo matching tablets) was mostly administered once daily before lunch, except on Day 56 when it was administered before breakfast and in fasted state on Day 84.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:
once daily oral dose of LIK066 0 mg

Number of subjects in period 1	LIK066 30 mg	LIK066 150 mg	Placebo
Started	43	43	21
Safety analysis set	43	43	21
Pharmacodynamics (PD) anlysis set	43	41	21
Completed	41	36	19
Not completed	2	7	2
Adverse event, non-fatal	1	1	1
Protocol deviation	1	3	-
Patient/guardian decision	-	3	-
Lost to follow-up	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	LIK066 30 mg
Reporting group description:	
Film coated tablet of LIK066 30 mg was mostly administered once daily before lunch, except on Day 56 when it was administered before breakfast and in fasted state on Day 84.	
Reporting group title	LIK066 150 mg
Reporting group description:	
Film coated tablet of LIK066 150 mg was mostly administered once daily before lunch, except on Day 56 when it was administered before breakfast and in fasted state on Day 84.	
Reporting group title	Placebo
Reporting group description:	
LIK066 0 mg film-coated tablet(Placebo matching tablets) was mostly administered once daily before lunch, except on Day 56 when it was administered before breakfast and in fasted state on Day 84.	

Reporting group values	LIK066 30 mg	LIK066 150 mg	Placebo
Number of subjects	43	43	21
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)	35	40	20
From 65-84 years	8	3	1
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	53.1	49.5	48.0
standard deviation	± 12.57	± 11.10	± 11.16
Sex: Female, Male Units: Participants			
Female	25	22	12
Male	18	21	9
Race/Ethnicity, Customized Units: Subjects			
White	34	35	17
Asian	8	4	3
Black or African American	1	3	1
Other	0	1	0

Reporting group values	Total		
Number of subjects	107		

Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	95		
From 65-84 years	12		
85 years and over	0		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Participants			
Female	59		
Male	48		
Race/Ethnicity, Customized Units: Subjects			
White	86		
Asian	15		
Black or African American	5		
Other	1		

End points

End points reporting groups

Reporting group title	LIK066 30 mg
Reporting group description:	
Film coated tablet of LIK066 30 mg was mostly administered once daily before lunch, except on Day 56 when it was administered before breakfast and in fasted state on Day 84.	
Reporting group title	LIK066 150 mg
Reporting group description:	
Film coated tablet of LIK066 150 mg was mostly administered once daily before lunch, except on Day 56 when it was administered before breakfast and in fasted state on Day 84.	
Reporting group title	Placebo
Reporting group description:	
LIK066 0 mg film-coated tablet(Placebo matching tablets) was mostly administered once daily before lunch, except on Day 56 when it was administered before breakfast and in fasted state on Day 84.	

Primary: Change from baseline in Alanine aminotransferase (ALT) at Week 12

End point title	Change from baseline in Alanine aminotransferase (ALT) at Week 12
End point description:	
Alanine aminotransferase (ALT) is an enzyme found primarily in the liver. ALT is increased with liver damage. In this study, the blood levels of ALT was used to detect liver injury. Baseline is defined as the mean of measurements taken at the Screening and Baseline visits.	
End point type	Primary
End point timeframe:	
Baseline, Week 12	

End point values	LIK066 30 mg	LIK066 150 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	34	20	
Units: Units per Liter (U/L)				
arithmetic mean (standard error)	-22.06 (± 4.16)	-30.41 (± 4.52)	-8.77 (± 5.99)	

Statistical analyses

Statistical analysis title	Change from baseline in ALT
Comparison groups	Placebo v LIK066 30 mg
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.075
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-13.29

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-22.8
upper limit	-3.78
Variability estimate	Standard error of the mean
Dispersion value	7.35

Statistical analysis title	Change from baseline in ALT
Comparison groups	LIK066 150 mg v Placebo
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-21.64
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-31.33
upper limit	-11.94
Variability estimate	Standard error of the mean
Dispersion value	7.49

Statistical analysis title	Change from baseline in ALT
Comparison groups	LIK066 30 mg v LIK066 150 mg
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.178
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	8.35
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.41
upper limit	16.29
Variability estimate	Standard error of the mean
Dispersion value	6.14

Secondary: Change from baseline in percent liver fat at Week 12

End point title	Change from baseline in percent liver fat at Week 12

End point description:

Percent (%) Liver fat was measured by Magnetic Resonance Imaging Proton Density Liver Fat Fraction(MRIPDFF). Patients underwent magnetic resonance imaging twice during the course of the study (baseline and end of treatment) to quantitate liver fat.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	LIK066 30 mg	LIK066 150 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	39	33	19	
Units: Percentage of Liver Fat				
arithmetic mean (standard error)	-4.40 (± 0.81)	-6.92 (± 0.87)	-2.67 (± 1.17)	

Statistical analyses

Statistical analysis title	Change from baseline in percent liver fat
Comparison groups	LIK066 30 mg v Placebo
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.235
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.73
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-3.6
upper limit	0.14
Variability estimate	Standard error of the mean
Dispersion value	1.45

Statistical analysis title	Change from baseline in percent liver fat
Comparison groups	LIK066 150 mg v Placebo
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-4.26

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-6.14
upper limit	-2.37
Variability estimate	Standard error of the mean
Dispersion value	1.46

Statistical analysis title	Change from baseline in percent liver fat
Comparison groups	LIK066 30 mg v LIK066 150 mg
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.037
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	2.52
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.98
upper limit	4.07
Variability estimate	Standard error of the mean
Dispersion value	1.19

Secondary: Percent change from baseline in total body weight at Week 12

End point title	Percent change from baseline in total body weight at Week 12
End point description:	
Body weight (to the nearest 0.1 kilogram [kg] was measured on a calibrated scale. The measurement was performed with the study subject in underwear and without shoes; or while wearing minimal indoor clothing.	
End point type	Secondary
End point timeframe:	
Baseline, Week 12	

End point values	LIK066 30 mg	LIK066 150 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	34	19	
Units: percentage				
arithmetic mean (standard error)	-3.48 (± 0.47)	-4.51 (± 0.52)	-0.33 (± 0.68)	

Statistical analyses

Statistical analysis title	Change from baseline in total body weight
Comparison groups	LIK066 30 mg v Placebo
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-3.15
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-4.22
upper limit	-2.08
Variability estimate	Standard error of the mean
Dispersion value	0.83

Statistical analysis title	Change from baseline in total body weight
Comparison groups	LIK066 150 mg v Placebo
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-4.18
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-5.28
upper limit	-3.08
Variability estimate	Standard error of the mean
Dispersion value	0.85

Statistical analysis title	Change from baseline in total body weight
Comparison groups	LIK066 30 mg v LIK066 150 mg
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.148
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	1.03

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.12
upper limit	1.94
Variability estimate	Standard error of the mean
Dispersion value	0.71

Secondary: Change from baseline in the Enhanced Liver Fibrosis Test score at week 12

End point title	Change from baseline in the Enhanced Liver Fibrosis Test score at week 12

End point description:

The Enhanced Liver Fibrosis (ELF) score is an ECM marker set consisting of tissue inhibitor of metalloproteinases 1 (TIMP-1), amino-terminal propeptide of type III procollagen (PIIINP) and hyaluronic acid (HA) showing good correlations with fibrosis stages in chronic liver disease.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	LIK066 30 mg	LIK066 150 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	34	21	
Units: Score				
arithmetic mean (standard deviation)	-0.2 (± 0.65)	-0.1 (± 0.61)	0.1 (± 0.37)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the concentration of Hyaluronic Acid at Week 12.

End point title	Change from baseline in the concentration of Hyaluronic Acid at Week 12.

End point description:

Hyaluronic Acid is a non-invasive marker of liver fibrosis. It was accessed by Enhanced liver fibrosis Test (ELF).

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	LIK066 30 mg	LIK066 150 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	34	21	
Units: ug/L				
arithmetic mean (standard deviation)	-3.4 (± 75.38)	0.4 (± 30.56)	4.7 (± 21.73)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the concentration of Procollagen Type Iii N-Terminal Peptide (PIIINP) at Week 12.

End point title	Change from baseline in the concentration of Procollagen Type Iii N-Terminal Peptide (PIIINP) at Week 12.

End point description:

PIIINP is a non-invasive marker of liver fibrosis. It was accessed by Enhanced liver fibrosis Test (ELF).

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	LIK066 30 mg	LIK066 150 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	34	20	
Units: ug/L				
arithmetic mean (standard deviation)	-1.7 (± 2.73)	-1.2 (± 3.66)	0.3 (± 1.88)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the concentration of Tissue Inhibitor Of Metalloproteinase 1 (TIMP-1) at Week 12.

End point title	Change from baseline in the concentration of Tissue Inhibitor Of Metalloproteinase 1 (TIMP-1) at Week 12.

End point description:

TIMP-1 is a non-invasive marker of liver fibrosis. It was accessed by Enhanced liver fibrosis Test (ELF).

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	LIK066 30 mg	LIK066 150 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	34	20	
Units: ug/L				
arithmetic mean (standard deviation)	-3.0 (± 38.98)	-10.9 (± 38.21)	10.3 (± 25.73)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics of LIK066: Observed maximum plasma concentration (Cmax) following drug administration

End point title	Pharmacokinetics of LIK066: Observed maximum plasma concentration (Cmax) following drug administration[1]

End point description:

Cmax is the observed maximum plasma concentration following drug administration (ng/mL)

End point type	Secondary

End point timeframe:

Day 56 (pre-dose and 1, 2, 4 and 6 hours post-dose)

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Placebo patients were excluded from the PK analyses

End point values	LIK066 30 mg	LIK066 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	32		
Units: ng/mL				
arithmetic mean (standard deviation)	405 (± 109)	1810 (± 729)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics of LIK066: Observed maximum time duration of maximum concentration (Tmax) following drug administration

End point title	Pharmacokinetics of LIK066: Observed maximum time duration of maximum concentration (Tmax) following drug administration[2]

End point description:

Tmax is the time to reach the maximum concentration after drug administration (hour). The time points presented are the actual and not the planned time points.

End point type	Secondary

End point timeframe:

Day 56 (pre-dose and 1, 2, 4 and 6 hours post-dose)

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Placebo patients were excluded from the PK analyses

End point values	LIK066 30 mg	LIK066 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	32		
Units: hours				
median (full range (min-max))	1.00 (0.500 to 6.00)	1.51 (0.567 to 6.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics of LIK066: Observed area under the curve up to the last measurable concentration (AUClast) following drug administration

End point title	Pharmacokinetics of LIK066: Observed area under the curve up to the last measurable concentration (AUClast) following drug administration[3]

End point description:

AUClast is the area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration (hour*ng/mL)

End point type	Secondary

End point timeframe:

Day 56 (pre-dose and 1, 2, 4 and 6 hours post-dose)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Placebo patients were excluded from the PK analyses

End point values	LIK066 30 mg	LIK066 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	32		
Units: hour*ng/mL				
arithmetic mean (standard deviation)	1280 (± 413)	5770 (± 1680)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Aspartate aminotransferase (AST) at Week 12

End point title	Change from baseline in Aspartate aminotransferase (AST) at Week 12

End point description:

Aspartate aminotransferase (AST) is an enzyme found in many cells of the body specifically those of the liver, heart and skeletal muscle. In healthy individuals, levels of AST in the blood are low. When liver or muscle cells are injured, they release AST into the blood. In this study, the blood levels of AST was used

to detect liver injury. Baseline is defined as the mean of measurements taken at the Screening and Baseline visits.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	LIK066 30 mg	LIK066 150 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	34	20	
Units: Units per liter (U/L)				
arithmetic mean (standard error)	-13.45 (± 2.46)	-17.01 (± 2.68)	-2.30 (± 3.54)	

Statistical analyses

Statistical analysis title	Change from baseline in AST
Comparison groups	LIK066 30 mg v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-11.15
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-16.79
upper limit	-5.5
Variability estimate	Standard error of the mean
Dispersion value	4.36

Statistical analysis title	Change from baseline in AST
Comparison groups	LIK066 150 mg v Placebo
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-14.71

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-20.43
upper limit	-8.98
Variability estimate	Standard error of the mean
Dispersion value	4.43

Statistical analysis title	Change from baseline in AST
Comparison groups	LIK066 30 mg v LIK066 150 mg
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.332
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	3.56
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.15
upper limit	8.28
Variability estimate	Standard error of the mean
Dispersion value	3.65

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from the first dose of study treatment until the end of study treatment i.e. Day 84 plus 28 days recovery and follow-up period.

Adverse event reporting additional description:

Any signs or symptoms that occured from the first dose of study treatment until the end of study treatment i.e. Day 84 plus 28 days recovery and follow-up period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo

Reporting group title	LIK066 30 mg

Reporting group description:

LIK066 30 mg

Reporting group title	LIK066 150 mg

Reporting group description:

LIK066 150 mg

Reporting group title	All Patients

Reporting group description:

All Patients

Serious adverse events	Placebo	LIK066 30 mg	LIK066 150 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 21 (4.76%)	0 / 43 (0.00%)	0 / 43 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
Gastroenteritis viral			
subjects affected / exposed	1 / 21 (4.76%)	0 / 43 (0.00%)	0 / 43 (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	All Patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 107 (0.93%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Infections and infestations			
Gastroenteritis viral			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo	LIK066 30 mg	LIK066 150 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 21 (85.71%)	31 / 43 (72.09%)	36 / 43 (83.72%)
Vascular disorders			
Diastolic hypotension			
subjects affected / exposed	0 / 21 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	0 / 21 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Peripheral coldness			
subjects affected / exposed	1 / 21 (4.76%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 21 (4.76%)	1 / 43 (2.33%)	1 / 43 (2.33%)
occurrences (all)	1	1	1
Chills			
subjects affected / exposed	1 / 21 (4.76%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Early satiety			
subjects affected / exposed	0 / 21 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	0 / 21 (0.00%)	2 / 43 (4.65%)	3 / 43 (6.98%)
occurrences (all)	0	2	3
Feeling hot			

subjects affected / exposed	1 / 21 (4.76%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Feeling jittery			
subjects affected / exposed	1 / 21 (4.76%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Hunger			
subjects affected / exposed	1 / 21 (4.76%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences (all)	1	0	1
Thirst			
subjects affected / exposed	0 / 21 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Vessel puncture site bruise			
subjects affected / exposed	0 / 21 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	1 / 21 (4.76%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Nipple pain			
subjects affected / exposed	0 / 21 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	2	0	0
Nasal congestion			
subjects affected / exposed	1 / 21 (4.76%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	1	1	0
Productive cough			
subjects affected / exposed	0 / 21 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Rhinorrhoea			

subjects affected / exposed	1 / 21 (4.76%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences (all)	1	0	1
Wheezing			
subjects affected / exposed	1 / 21 (4.76%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 21 (0.00%)	2 / 43 (4.65%)	0 / 43 (0.00%)
occurrences (all)	0	2	0
Depression			
subjects affected / exposed	0 / 21 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Mood swings			
subjects affected / exposed	0 / 21 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Nervousness			
subjects affected / exposed	0 / 21 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 21 (0.00%)	2 / 43 (4.65%)	0 / 43 (0.00%)
occurrences (all)	0	2	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 21 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Blood bilirubin increased			
subjects affected / exposed	0 / 21 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Blood cholesterol increased			
subjects affected / exposed	0 / 21 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Blood triglycerides increased			

subjects affected / exposed	0 / 21 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 21 (4.76%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Heart rate irregular			
subjects affected / exposed	0 / 21 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Lymphocyte morphology abnormal			
subjects affected / exposed	0 / 21 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 21 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Joint injury			
subjects affected / exposed	0 / 21 (0.00%)	2 / 43 (4.65%)	0 / 43 (0.00%)
occurrences (all)	0	2	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 21 (4.76%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences (all)	1	0	2
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 21 (14.29%)	0 / 43 (0.00%)	4 / 43 (9.30%)
occurrences (all)	4	0	7
Head discomfort			
subjects affected / exposed	0 / 21 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	3 / 21 (14.29%)	2 / 43 (4.65%)	5 / 43 (11.63%)
occurrences (all)	3	2	13
Hypoaesthesia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Somnolence			

subjects affected / exposed	0 / 21 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Tremor			
subjects affected / exposed	1 / 21 (4.76%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 21 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Glaucoma			
subjects affected / exposed	0 / 21 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 21 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Abdominal distension			
subjects affected / exposed	0 / 21 (0.00%)	2 / 43 (4.65%)	6 / 43 (13.95%)
occurrences (all)	0	2	7
Abdominal pain			
subjects affected / exposed	2 / 21 (9.52%)	1 / 43 (2.33%)	5 / 43 (11.63%)
occurrences (all)	2	1	10
Abdominal pain upper			
subjects affected / exposed	2 / 21 (9.52%)	0 / 43 (0.00%)	3 / 43 (6.98%)
occurrences (all)	2	0	3
Abdominal tenderness			
subjects affected / exposed	0 / 21 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Anal pruritus			
subjects affected / exposed	0 / 21 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Colitis			

subjects affected / exposed	0 / 21 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	1 / 21 (4.76%)	2 / 43 (4.65%)	3 / 43 (6.98%)
occurrences (all)	1	2	3
Diarrhoea			
subjects affected / exposed	9 / 21 (42.86%)	21 / 43 (48.84%)	33 / 43 (76.74%)
occurrences (all)	30	51	191
Dyspepsia			
subjects affected / exposed	1 / 21 (4.76%)	1 / 43 (2.33%)	1 / 43 (2.33%)
occurrences (all)	1	1	2
Flatulence			
subjects affected / exposed	2 / 21 (9.52%)	2 / 43 (4.65%)	8 / 43 (18.60%)
occurrences (all)	2	2	12
Gastric dilatation			
subjects affected / exposed	0 / 21 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Gastric ulcer			
subjects affected / exposed	1 / 21 (4.76%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 21 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Haemorrhoids			
subjects affected / exposed	0 / 21 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Large intestine polyp			
subjects affected / exposed	0 / 21 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	3 / 21 (14.29%)	4 / 43 (9.30%)	3 / 43 (6.98%)
occurrences (all)	3	5	4
Toothache			
subjects affected / exposed	0 / 21 (0.00%)	1 / 43 (2.33%)	1 / 43 (2.33%)
occurrences (all)	0	1	1
Vomiting			

subjects affected / exposed	2 / 21 (9.52%)	5 / 43 (11.63%)	2 / 43 (4.65%)
occurrences (all)	4	5	3
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 21 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Hepatic cirrhosis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Portal hypertension			
subjects affected / exposed	1 / 21 (4.76%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Night sweats			
subjects affected / exposed	1 / 21 (4.76%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Papule			
subjects affected / exposed	0 / 21 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Ketonuria			
subjects affected / exposed	0 / 21 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Microalbuminuria			
subjects affected / exposed	0 / 21 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Nocturia			
subjects affected / exposed	0 / 21 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Polyuria			
subjects affected / exposed	1 / 21 (4.76%)	4 / 43 (9.30%)	1 / 43 (2.33%)
occurrences (all)	1	4	1
Proteinuria			

subjects affected / exposed	0 / 21 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Urinary incontinence			
subjects affected / exposed	0 / 21 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 21 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Arthritis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 43 (2.33%)	1 / 43 (2.33%)
occurrences (all)	0	1	1
Back pain			
subjects affected / exposed	1 / 21 (4.76%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences (all)	2	0	1
Muscle spasms			
subjects affected / exposed	2 / 21 (9.52%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences (all)	2	0	4
Muscular weakness			
subjects affected / exposed	0 / 21 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Musculoskeletal chest pain			
subjects affected / exposed	1 / 21 (4.76%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	2 / 21 (9.52%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	2	0	0
Neck pain			
subjects affected / exposed	1 / 21 (4.76%)	1 / 43 (2.33%)	2 / 43 (4.65%)
occurrences (all)	1	1	2
Osteitis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			

Bronchitis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Fungal infection			
subjects affected / exposed	0 / 21 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Furuncle			
subjects affected / exposed	1 / 21 (4.76%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	1	1	0
Gastroenteritis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 43 (2.33%)	1 / 43 (2.33%)
occurrences (all)	0	1	1
Gastroenteritis viral			
subjects affected / exposed	1 / 21 (4.76%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Gingival abscess			
subjects affected / exposed	0 / 21 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	0 / 21 (0.00%)	4 / 43 (9.30%)	0 / 43 (0.00%)
occurrences (all)	0	5	0
Nasopharyngitis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 43 (0.00%)	3 / 43 (6.98%)
occurrences (all)	1	0	3
Oral herpes			
subjects affected / exposed	1 / 21 (4.76%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Otitis externa			
subjects affected / exposed	0 / 21 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Rhinitis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Sinusitis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0

Upper respiratory tract infection			
subjects affected / exposed	1 / 21 (4.76%)	3 / 43 (6.98%)	0 / 43 (0.00%)
occurrences (all)	1	4	0
Urinary tract infection			
subjects affected / exposed	1 / 21 (4.76%)	2 / 43 (4.65%)	0 / 43 (0.00%)
occurrences (all)	1	2	0
Vaginal infection			
subjects affected / exposed	0 / 21 (0.00%)	0 / 43 (0.00%)	2 / 43 (4.65%)
occurrences (all)	0	0	3
Viral infection			
subjects affected / exposed	0 / 21 (0.00%)	0 / 43 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 21 (0.00%)	0 / 43 (0.00%)	2 / 43 (4.65%)
occurrences (all)	0	0	3
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 21 (4.76%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	1	1	0
Diabetes mellitus			
subjects affected / exposed	0 / 21 (0.00%)	1 / 43 (2.33%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Food craving			
subjects affected / exposed	1 / 21 (4.76%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Hypercholesterolaemia			
subjects affected / exposed	1 / 21 (4.76%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Hypoglycaemia			
subjects affected / exposed	1 / 21 (4.76%)	2 / 43 (4.65%)	0 / 43 (0.00%)
occurrences (all)	1	2	0
Hypovitaminosis			
subjects affected / exposed	1 / 21 (4.76%)	0 / 43 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Polydipsia			

subjects affected / exposed	0 / 21 (0.00%)	2 / 43 (4.65%)	1 / 43 (2.33%)
occurrences (all)	0	2	1

Non-serious adverse events	All Patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	85 / 107 (79.44%)		
Vascular disorders			
Diastolic hypotension			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		
Peripheral coldness			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 107 (2.80%)		
occurrences (all)	3		
Chills			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		
Early satiety			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	5 / 107 (4.67%)		
occurrences (all)	5		
Feeling hot			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		
Feeling jittery			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		
Hunger			

subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	2 / 107 (1.87%)		
occurrences (all)	2		
Thirst			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		
Vessel puncture site bruise			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		
Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Nipple pain			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	2		
Nasal congestion			
subjects affected / exposed	2 / 107 (1.87%)		
occurrences (all)	2		
Productive cough			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	2 / 107 (1.87%)		
occurrences (all)	2		
Wheezing			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		
Psychiatric disorders			

Anxiety				
subjects affected / exposed	2 / 107 (1.87%)			
occurrences (all)	2			
Depression				
subjects affected / exposed	1 / 107 (0.93%)			
occurrences (all)	1			
Insomnia				
subjects affected / exposed	1 / 107 (0.93%)			
occurrences (all)	1			
Mood swings				
subjects affected / exposed	1 / 107 (0.93%)			
occurrences (all)	1			
Nervousness				
subjects affected / exposed	1 / 107 (0.93%)			
occurrences (all)	1			
Investigations				
Alanine aminotransferase increased				
subjects affected / exposed	2 / 107 (1.87%)			
occurrences (all)	2			
Aspartate aminotransferase increased				
subjects affected / exposed	1 / 107 (0.93%)			
occurrences (all)	1			
Blood bilirubin increased				
subjects affected / exposed	1 / 107 (0.93%)			
occurrences (all)	1			
Blood cholesterol increased				
subjects affected / exposed	1 / 107 (0.93%)			
occurrences (all)	1			
Blood triglycerides increased				
subjects affected / exposed	1 / 107 (0.93%)			
occurrences (all)	1			
Electrocardiogram QT prolonged				
subjects affected / exposed	1 / 107 (0.93%)			
occurrences (all)	1			
Heart rate irregular				

subjects affected / exposed occurrences (all) Lymphocyte morphology abnormal subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1 1 / 107 (0.93%) 1		
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all) Joint injury subjects affected / exposed occurrences (all)	 1 / 107 (0.93%) 1 2 / 107 (1.87%) 2		
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	 2 / 107 (1.87%) 3		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Head discomfort subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Hypoaesthesia subjects affected / exposed occurrences (all) Somnolence subjects affected / exposed occurrences (all) Tremor subjects affected / exposed occurrences (all)	 7 / 107 (6.54%) 11 1 / 107 (0.93%) 1 10 / 107 (9.35%) 18 1 / 107 (0.93%) 1 1 / 107 (0.93%) 1 1 / 107 (0.93%) 1		
Blood and lymphatic system disorders			

Neutropenia subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Eye disorders Glaucoma subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Abdominal distension subjects affected / exposed occurrences (all)	8 / 107 (7.48%) 9		
Abdominal pain subjects affected / exposed occurrences (all)	8 / 107 (7.48%) 13		
Abdominal pain upper subjects affected / exposed occurrences (all)	5 / 107 (4.67%) 5		
Abdominal tenderness subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Anal pruritus subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Colitis subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Constipation subjects affected / exposed occurrences (all)	6 / 107 (5.61%) 6		
Diarrhoea			

subjects affected / exposed	63 / 107 (58.88%)		
occurrences (all)	272		
Dyspepsia			
subjects affected / exposed	3 / 107 (2.80%)		
occurrences (all)	4		
Flatulence			
subjects affected / exposed	12 / 107 (11.21%)		
occurrences (all)	16		
Gastric dilatation			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		
Gastric ulcer			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		
Haemorrhoids			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		
Large intestine polyp			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	10 / 107 (9.35%)		
occurrences (all)	12		
Toothache			
subjects affected / exposed	2 / 107 (1.87%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	9 / 107 (8.41%)		
occurrences (all)	12		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		

Hepatic cirrhosis subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Portal hypertension subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Night sweats subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Papule subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Renal and urinary disorders			
Ketonuria subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Microalbuminuria subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Nocturia subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Polyuria subjects affected / exposed occurrences (all)	6 / 107 (5.61%) 6		
Proteinuria subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Urinary incontinence subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Musculoskeletal and connective tissue disorders			

Arthralgia subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Arthritis subjects affected / exposed occurrences (all)	2 / 107 (1.87%) 2		
Back pain subjects affected / exposed occurrences (all)	2 / 107 (1.87%) 3		
Muscle spasms subjects affected / exposed occurrences (all)	3 / 107 (2.80%) 6		
Muscular weakness subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Myalgia subjects affected / exposed occurrences (all)	2 / 107 (1.87%) 2		
Neck pain subjects affected / exposed occurrences (all)	4 / 107 (3.74%) 4		
Osteitis subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Fungal infection subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1		
Furuncle			

subjects affected / exposed	2 / 107 (1.87%)			
occurrences (all)	2			
Gastroenteritis				
subjects affected / exposed	2 / 107 (1.87%)			
occurrences (all)	2			
Gastroenteritis viral				
subjects affected / exposed	1 / 107 (0.93%)			
occurrences (all)	1			
Gingival abscess				
subjects affected / exposed	1 / 107 (0.93%)			
occurrences (all)	1			
Influenza				
subjects affected / exposed	4 / 107 (3.74%)			
occurrences (all)	5			
Nasopharyngitis				
subjects affected / exposed	4 / 107 (3.74%)			
occurrences (all)	4			
Oral herpes				
subjects affected / exposed	1 / 107 (0.93%)			
occurrences (all)	1			
Otitis externa				
subjects affected / exposed	1 / 107 (0.93%)			
occurrences (all)	1			
Rhinitis				
subjects affected / exposed	1 / 107 (0.93%)			
occurrences (all)	1			
Sinusitis				
subjects affected / exposed	1 / 107 (0.93%)			
occurrences (all)	1			
Upper respiratory tract infection				
subjects affected / exposed	4 / 107 (3.74%)			
occurrences (all)	5			
Urinary tract infection				
subjects affected / exposed	3 / 107 (2.80%)			
occurrences (all)	3			
Vaginal infection				

subjects affected / exposed	2 / 107 (1.87%)		
occurrences (all)	3		
Viral infection			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		
Vulvovaginal mycotic infection			
subjects affected / exposed	2 / 107 (1.87%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 107 (1.87%)		
occurrences (all)	2		
Diabetes mellitus			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		
Food craving			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		
Hypercholesterolaemia			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		
Hypoglycaemia			
subjects affected / exposed	3 / 107 (2.80%)		
occurrences (all)	3		
Hypovitaminosis			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences (all)	1		
Polydipsia			
subjects affected / exposed	3 / 107 (2.80%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 September 2017	The purpose of this amendment was to include additional exclusion criteria and patient safety information. This was based on the newly emerging safety data and regulatory guidance. The below exclusion criteria were added: - history of ketoacidosis, lactic acidosis or hyperosmolar coma - history of lower limb amputation
11 February 2019	The purpose of this amendment was to include additional information on risks and patient safety. This was based on newly emerging safety data and regulatory safety warning about SGLT2 inhibitors. Fournier's gangrene was added to the exclusion criteria.
29 August 2019	The purpose of this amendment was to update the language related to sharing the study results from the second interim analysis. This allowed the Sponsor to share the aggregate results from interim analysis of this ongoing study with Investigators and scientific community. Because, the study was fully recruited and had more than 88 patients who had completed the study (as defined in the protocol) by the time the aggregate results were released no impact on patient safety and data integrity was anticipated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported