



Clinical trial results:

A Randomized, Patient and Investigator Blinded, Placebo Controlled, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics and Efficacy of LMB763 in Patients With Non-alcoholic Steatohepatitis (NASH)

Summary

EudraCT number	2016-002833-31
Trial protocol	GB
Global end of trial date	04 March 2019

Results information

Result version number	v1 (current)
This version publication date	09 October 2019
First version publication date	09 October 2019

Trial information

Trial identification

Sponsor protocol code	CLMB763X2201
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02913105
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 Pharmaceuticals AG, +41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharmaceuticals AG, +41 613241111,

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	04 March 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 March 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

- To determine the safety and tolerability of LMB763 during 12 weeks of treatment
- To determine the effect of LMB763 on circulating alanine aminotransferase (ALT) levels

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	24 October 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	Australia: 3
Country: Number of subjects enrolled	Jordan: 15
Country: Number of subjects enrolled	New Zealand: 21
Country: Number of subjects enrolled	Switzerland: 7
Country: Number of subjects enrolled	United States: 72
Country: Number of subjects enrolled	United Kingdom: 3
Worldwide total number of subjects	121
EEA total number of subjects	3

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)	110
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 25 centres across 6 countries.

Pre-assignment

Screening details:

A total of 121 subjects were enrolled in the study, and included in the safety population. Placebo data have been pooled from placebo treated subjects from both cohorts (100 mg and 50 mg matching placebo).

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

Arms

Are arms mutually exclusive?	Yes
Arm title	LMB763 100 mg

Arm description:

LMB763 100 mg capsules, orally, once daily for 12 weeks (84 days) under fasted conditions (no food or drink for at least 6 hours).

Arm type	Experimental
Investigational medicinal product name	LMB763 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

LMB763 100 mg capsules, orally, once daily for 12 weeks (84 days) under fasted conditions (no food or drink for at least 6 hours).

Arm title	LMB763 50 mg
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Arm description:

LMB763 50 mg (2 x 25 mg) capsules, orally, once daily for 12 weeks (84 days) under fasted conditions (no food or drink for at least 6 hours).

Arm type	Experimental
Investigational medicinal product name	LMB763 50 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

LMB763 50 mg (2 x 25 mg) capsules, orally, once daily for 12 weeks (84 days) under fasted conditions (no food or drink for at least 6 hours).

Arm title	Pooled Placebo
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Arm description:

LMB763 100 mg or 50 mg matching placebo capsules, orally, once daily for 12 weeks (84 days) under fasted conditions (no food or drink for at least 6 hours).

Arm type	Placebo
Investigational medicinal product name	Pooled Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

LMB763 100 mg or 50 mg matching placebo capsules, orally, once daily for 12 weeks (84 days) under fasted conditions (no food or drink for at least 6 hours)

Number of subjects in period 1	LMB763 100 mg	LMB763 50 mg	Pooled Placebo
Started	37	44	40
Completed	22	39	33
Not completed	15	5	7
Physician decision	1	1	-
Adverse event, non-fatal	11	-	4
Reason Not Specified	3	1	1
Non-Compliance With Study Drug	-	-	1
Withdrawal by Subject	-	3	1

Baseline characteristics

Reporting groups

Reporting group title	LMB763 100 mg
Reporting group description: LMB763 100 mg capsules, orally, once daily for 12 weeks (84 days) under fasted conditions (no food or drink for at least 6 hours).	
Reporting group title	LMB763 50 mg
Reporting group description: LMB763 50 mg (2 x 25 mg) capsules, orally, once daily for 12 weeks (84 days) under fasted conditions (no food or drink for at least 6 hours).	
Reporting group title	Pooled Placebo
Reporting group description: LMB763 100 mg or 50 mg matching placebo capsules, orally, once daily for 12 weeks (84 days) under fasted conditions (no food or drink for at least 6 hours).	

Reporting group values	LMB763 100 mg	LMB763 50 mg	Pooled Placebo
Number of subjects	37	44	40
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)	30	44	36
From 65-84 years	7	0	4
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	51.3	49.5	51.6
standard deviation	± 15.55	± 8.45	± 11.65
Gender categorical Units: Subjects			
Female	22	23	24
Male	15	21	16

Reporting group values	Total		
Number of subjects	121		
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)	110		
From 65-84 years	11		
85 years and over	0		
Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	69		
Male	52		

End points

End points reporting groups

Reporting group title	LMB763 100 mg
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Reporting group description:

LMB763 100 mg capsules, orally, once daily for 12 weeks (84 days) under fasted conditions (no food or drink for at least 6 hours).

Reporting group title	LMB763 50 mg
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Reporting group description:

LMB763 50 mg (2 x 25 mg) capsules, orally, once daily for 12 weeks (84 days) under fasted conditions (no food or drink for at least 6 hours).

Reporting group title	Pooled Placebo
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Reporting group description:

LMB763 100 mg or 50 mg matching placebo capsules, orally, once daily for 12 weeks (84 days) under fasted conditions (no food or drink for at least 6 hours).

Subject analysis set title	LMB763 100 mg
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Pharmacokinetic (PK) analysis set included all subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations that impact on PK data.

Subject analysis set title	LMB763 50 mg
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

PK analysis set included all subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations that impact on PK data.

Primary: Number of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs) ^[1]
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End point description:

An AE is defined as any untoward medical occurrence in a clinical study subject, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. An SAE is defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent disability/incapacity, is a congenital anomaly/birth defect or any other situation as per Medical or scientific judgment. Safety analysis set included all subjects that received at least one dose of study drug.

End point type	Primary
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End point timeframe:

From date of first subject first treatment until Last Patient Last Visit (LPLV) (up to Day 112 (End of Study (EOS))

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: No statistical analysis was planned for this end point

End point values	LMB763 100 mg	LMB763 50 mg	Pooled Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37 ^[2]	44 ^[3]	40 ^[4]	
Units: subjects				
AEs	35	37	33	
SAEs	2	3	0	

Notes:

[2] - Safety analysis set.

[3] - Safety analysis set.

[4] - Safety analysis set.

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Alanine Aminotransferase (ALT) Levels

End point title	Change From Baseline in Alanine Aminotransferase (ALT) Levels
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End point description:

ALT level assessment was one of the diagnostic parameters in Liver function test (LFT). Baseline was defined as the mean of ALT levels at baseline and pre-dose visits. Geometric Mean and Geometric Coefficient of Variation for change are based on log-transformed ratio to baseline (i.e., change from baseline in the log domain). Pharmacodynamic (PD) analysis set included all subjects with available PD data and no protocol deviations with relevant impact on PD data. 'n' represents the number of subjects in each category with a value at both Baseline and that time point.

End point type	Primary
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End point timeframe:

Baseline to Day 84 (Week 12)

End point values	LMB763 100 mg	LMB763 50 mg	Pooled Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37 ^[5]	44 ^[6]	40 ^[7]	
Units: units per litre (U/L)				
geometric mean (geometric coefficient of variation)				
Baseline for Day 84 Analysis	67.215 (± 30.8)	48.114 (± 42.2)	59.544 (± 39.5)	
Change from Baseline at Day 84	0.667 (± 33.8)	0.702 (± 41.1)	0.901 (± 25.5)	

Notes:

[5] - PD analysis set: n = 24, 24

[6] - PD analysis set: n = 40, 40

[7] - PD analysis set: n = 33, 33

Statistical analyses

Statistical analysis title	LMB763 100 mg, LMB763 50 mg
Comparison groups	LMB763 100 mg v LMB763 50 mg

Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	other ^[8]
P-value	= 0.7489 ^[9]
Method	ANCOVA
Parameter estimate	Geometric Mean Ratios
Point estimate	0.97
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.83
upper limit	1.13

Notes:

[8] - Log transformed ratio to baseline was analyzed using a repeated measures model which included effects for treatment, visit, treatment by visit interaction, stratification factor (Body Mass Index (BMI) group), log-transformed baseline and log-transformed baseline by visit interaction. BMI was separated into two groups low BMI (Asian<30 and Non-Asian<35) and high BMI (Asian >=30 and Non-Asian>=35).

[9] - An unstructured variance-covariance structure was used.

Statistical analysis title	LMB763 100 mg, Pooled Placebo
Comparison groups	LMB763 100 mg v Pooled Placebo
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority ^[10]
P-value	= 0.0005 ^[11]
Method	ANCOVA
Parameter estimate	Geometric Mean Ratios
Point estimate	0.72
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.62
upper limit	0.84

Notes:

[10] - Log transformed ratio to baseline was analyzed using a repeated measures model which included effects for treatment, visit, treatment by visit interaction, stratification factor (BMI group), log-transformed baseline and log-transformed baseline by visit interaction. BMI was separated into two groups low BMI (Asian<30 and Non-Asian<35) and high BMI (Asian >=30 and Non-Asian>=35).

[11] - An unstructured variance-covariance structure was used.

Statistical analysis title	LMB763 50 mg, Pooled Placebo
Comparison groups	LMB763 50 mg v Pooled Placebo
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority ^[12]
P-value	= 0.0005 ^[13]
Method	ANCOVA
Parameter estimate	Geometric Mean Ratios
Point estimate	0.74

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.65
upper limit	0.85

Notes:

[12] - Log transformed ratio to baseline was analyzed using a repeated measures model which included effects for treatment, visit, treatment by visit interaction, stratification factor (BMI group), log-transformed baseline and log-transformed baseline by visit interaction. BMI was separated into two groups low BMI (Asian<30 and Non-Asian<35) and high BMI (Asian ≥30 and Non-Asian≥35).

[13] - An unstructured variance-covariance structure was used.

Secondary: Observed Maximum Plasma Concentration (Cmax) of LMB763

End point title	Observed Maximum Plasma Concentration (Cmax) of LMB763
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End point description:

PK analysis set included all subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations that impact on PK data. 'n' represents the number of subjects in each category with a value at both Baseline and that time point.

End point type	Secondary
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End point timeframe:

Days 1 and 42

End point values	LMB763 100 mg	LMB763 50 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37 ^[14]	43 ^[15]		
Units: nanograms per millilitre (ng/mL)				
arithmetic mean (standard deviation)				
Day 1	3080 (± 1360)	1290 (± 620)		
Day 42	2230 (± 1190)	1290 (± 690)		

Notes:

[14] - PK analysis set: n = 37, 23

[15] - PK analysis set: n = 43, 42

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Concentration (Tmax) of LMB763

End point title	Time to Reach Maximum Concentration (Tmax) of LMB763
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End point description:

PK analysis set included all subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations that impact on PK data. 'n' represents the number of subjects in each category with a value at both Baseline and that time point.

End point type	Secondary
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End point timeframe:

Days 1 and 42

End point values	LMB763 100 mg	LMB763 50 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37 ^[16]	43 ^[17]		
Units: hour (h)				
median (full range (min-max))				
Day 1	2.00 (1.00 to 6.00)	2.00 (1.00 to 6.08)		
Day 42	2.03 (1.00 to 6.03)	2.02 (1.00 to 6.00)		

Notes:

[16] - Pk analysis set: n = 37, 24

[17] - Pk analysis set: n = 43, 42

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under Plasma Concentration-time Curve From Time Zero to Time of Last Quantifiable Concentration (AUClast) of LMB763

End point title	Area Under Plasma Concentration-time Curve From Time Zero to Time of Last Quantifiable Concentration (AUClast) of LMB763
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End point description:

PK analysis set included all subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations that impact on PK data. 'n' represents the number of subjects in each category with a value at both Baseline and that time point.

End point type	Secondary
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End point timeframe:

Days 1 and 42

End point values	LMB763 100 mg	LMB763 50 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37 ^[18]	43 ^[19]		
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Day 1	11200 (± 4740)	4360 (± 2350)		
Day 42	8570 (± 4120)	5180 (± 2870)		

Notes:

[18] - Pk analysis set: n = 37, 23

[19] - Pk analysis set: n = 42, 42

Statistical analyses

No statistical analyses for this end point

Secondary: Accumulation Ratio (Racc) of LMB763

End point title	Accumulation Ratio (Racc) of LMB763
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End point description:

PK analysis set included all subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations that impact on PK data.

End point type	Secondary
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End point timeframe:

Day 42

End point values	LMB763 100 mg	LMB763 50 mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24 ^[20]	42 ^[21]		
Units: ratio				
arithmetic mean (standard deviation)	0.903 (± 0.472)	1.31 (± 0.641)		

Notes:

[20] - PD analysis set.

[21] - PD analysis set.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Percentage of Liver Fat as Measured by Magnetic Resonance Imaging (MRI)

End point title	Change From Baseline in Percentage of Liver Fat as Measured by Magnetic Resonance Imaging (MRI)
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End point description:

Subjects were to undergo MRI twice (Baseline and End of Treatment) during the course of the study to quantitate liver fat. Baseline was defined as the last available measurement prior to the first dose. Geometric Mean and Geometric Coefficient of Variation for change are based on log-transformed ratio to baseline (i.e., change from baseline in the log domain). PD analysis set included all subjects with available PD data and no protocol deviations with relevant impact on PD data. 'n' represents the number of subjects in each category with a value at both Baseline and that time point.

End point type	Secondary
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End point timeframe:

Baseline to Day 84 (Week 12)

End point values	LMB763 100 mg	LMB763 50 mg	Pooled Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	35 ^[22]	44 ^[23]	39 ^[24]	
Units: percentage of liver fat				
geometric mean (geometric coefficient of variation)				

Baseline for Day 84 Analysis	18.751 (\pm 37.4)	17.715 (\pm 42.6)	17.476 (\pm 73.9)	
Change from Baseline at Day 84	0.648 (\pm 29.3)	0.681 (\pm 38.6)	0.962 (\pm 22.2)	

Notes:

[22] - PD analysis set: n = 22, 22

[23] - PD analysis set: n = 41, 41

[24] - PD analysis set: n = 32, 32

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Weight

End point title	Change From Baseline in Weight
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End point description:

Baseline was defined as the last available measurement prior to the first dose. PD analysis set included all subjects with available PD data and no protocol deviations with relevant impact on PD data. 'n' represents the number of subjects in each category with a value at both Baseline and that time point.

End point type	Secondary
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End point timeframe:

Baseline to Days 28, 42, 56, 84 and 112 (EOS)

End point values	LMB763 100 mg	LMB763 50 mg	Pooled Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37 ^[25]	44 ^[26]	40 ^[27]	
Units: kilogram (kg)				
arithmetic mean (standard deviation)				
Baseline for Day 28 Analysis	99.07 (\pm 22.560)	97.82 (\pm 17.829)	95.47 (\pm 22.921)	
Change from Baseline at Day 28	-0.78 (\pm 1.591)	-0.71 (\pm 1.725)	-0.17 (\pm 1.516)	
Baseline for Day 42 Analysis	96.89 (\pm 22.135)	97.82 (\pm 17.829)	95.30 (\pm 23.465)	
Change from Baseline at Day 42	-1.04 (\pm 1.683)	-1.08 (\pm 2.335)	-0.24 (\pm 1.677)	
Baseline for Day 56 Analysis	97.07 (\pm 22.555)	97.86 (\pm 18.043)	95.71 (\pm 23.244)	
Change from Baseline at Day 56	-1.39 (\pm 1.970)	-1.39 (\pm 2.188)	-0.26 (\pm 1.777)	
Baseline for Day 84 Analysis	97.34 (\pm 23.370)	97.11 (\pm 17.905)	95.91 (\pm 23.563)	
Change from Baseline at Day 84	-1.47 (\pm 2.169)	-2.02 (\pm 3.451)	-0.21 (\pm 1.989)	
Baseline for Day 112 (EOS) Analysis	98.74 (\pm 23.941)	95.38 (\pm 14.810)	95.85 (\pm 23.926)	
Change from Baseline at Day 112 (EOS)	-1.26 (\pm 3.014)	-1.66 (\pm 3.543)	0.35 (\pm 2.125)	

Notes:

[25] - PD analysis set. n = 30, 30, 27, 27, 26, 26, 24, 24, 22, 22

[26] - PD analysis set. n = 43, 43, 43, 43, 42, 42, 40, 40, 39, 39

[27] - PD analysis set. n = 37, 37, 34, 34, 35, 35, 34, 34, 33, 33

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Body Mass Index (BMI)

End point title	Change From Baseline in Body Mass Index (BMI)
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End point description:

Baseline was defined as the last available measurement prior to the first dose at specified visit (day). PD analysis set included all subjects with available PD data and no protocol deviations with relevant impact on PD data. 'n' represents the number of subjects in each category with a value at both Baseline and that time point.

End point type	Secondary
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End point timeframe:

Baseline to Days 28, 42, 56, 84 and 112 (EOS)

End point values	LMB763 100 mg	LMB763 50 mg	Pooled Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37 ^[28]	44 ^[29]	40 ^[30]	
Units: kilograms per metre square (kg/m ²)				
arithmetic mean (standard deviation)				
Baseline for Day 28 Analysis	34.81 (± 5.641)	34.41 (± 5.270)	34.93 (± 5.180)	
Change from Baseline at Day 28	-0.29 (± 0.545)	-0.26 (± 0.638)	-0.05 (± 0.511)	
Baseline for Day 42 Analysis	34.05 (± 5.162)	34.41 (± 5.270)	34.56 (± 5.233)	
Change from Baseline at Day 42	-0.36 (± 0.591)	-0.40 (± 0.845)	-0.08 (± 0.572)	
Baseline for Day 56 Analysis	34.12 (± 5.253)	34.37 (± 5.327)	34.75 (± 5.269)	
Change from Baseline at Day 56	-0.50 (± 0.688)	-0.49 (± 0.799)	-0.10 (± 0.663)	
Baseline for Day 84 Analysis	34.18 (± 5.467)	34.04 (± 5.190)	34.89 (± 5.275)	
Change from Baseline at Day 84	-0.52 (± 0.764)	-0.72 (± 1.215)	-0.09 (± 0.718)	
Baseline for Day 112 (EOS) Analysis	34.60 (± 5.522)	33.82 (± 4.980)	34.96 (± 5.342)	
Change from Baseline at Day 112 (EOS)	-0.45 (± 0.974)	-0.60 (± 1.276)	0.12 (± 0.776)	

Notes:

[28] - PD analysis set. n = 30, 30, 27, 27, 26, 26, 24, 24, 22, 22

[29] - PD analysis set. n = 43, 43, 43, 43, 42, 42, 40, 40, 39, 39

[30] - PD analysis set. n = 37, 37, 34, 34, 35, 35, 34, 34, 33, 33

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Waist to Hip Ratio

End point title	Change From Baseline in Waist to Hip Ratio
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End point description:

Baseline was defined as the last available measurement prior to the first dose. PD analysis set included all subjects with available PD data and no protocol deviations with relevant impact on PD data. 'n' represents the number of subjects in each category with a value at both Baseline and that time point.

End point type	Secondary
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End point timeframe:

Baseline to Days 28, 42, 56, 84 and 112 (EOS)

End point values	LMB763 100 mg	LMB763 50 mg	Pooled Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37 ^[31]	44 ^[32]	40 ^[33]	
Units: ratio				
arithmetic mean (standard deviation)				
Baseline for Day 28 Analysis	0.96 (± 0.065)	0.96 (± 0.055)	0.95 (± 0.089)	
Change from Baseline at Day 28	0.00 (± 0.039)	0.00 (± 0.034)	-0.00 (± 0.039)	
Baseline for Day 42 Analysis	0.96 (± 0.061)	0.95 (± 0.056)	0.96 (± 0.086)	
Change from Baseline at Day 42	0.01 (± 0.077)	-0.00 (± 0.039)	0.00 (± 0.036)	
Baseline for Day 56 Analysis	0.96 (± 0.061)	0.96 (± 0.054)	0.96 (± 0.087)	
Change from Baseline at Day 56	-0.00 (± 0.029)	-0.00 (± 0.033)	-0.01 (± 0.029)	
Baseline for Day 84 Analysis	0.95 (± 0.063)	0.96 (± 0.055)	0.96 (± 0.087)	
Change from Baseline at Day 84	0.00 (± 0.043)	-0.01 (± 0.044)	0.01 (± 0.046)	
Baseline for Day 112 (EOS) Analysis	0.96 (± 0.059)	0.96 (± 0.054)	0.96 (± 0.087)	
Change from Baseline at Day 112 (EOS)	-0.00 (± 0.030)	0.00 (± 0.050)	-0.00 (± 0.037)	

Notes:

[31] - PD analysis set. n = 30, 30, 27, 27, 25, 25, 24, 24, 22, 22

[32] - PD analysis set. n = 43, 43, 40, 40, 42, 42, 40, 40, 39, 39

[33] - PD analysis set. n = 36, 36, 34, 34, 34, 34, 34, 34, 33, 33

Statistical analyses

No statistical analyses for this end point

Secondary: Change From to Baseline in Liver Stiffness

End point title	Change From to Baseline in Liver Stiffness
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End point description:

Fibroscan® was performed where available to assess liver stiffness. Baseline was defined as the last available measurement prior to the first dose. Geometric Mean and Geometric Coefficient of Variation for change are based on log-transformed ratio to baseline (i.e., change from baseline in the log domain). PD analysis set included all subjects with available PD data and no protocol deviations with relevant impact on PD data. 'n' represents the number of subjects in each category with a value at both Baseline and that time point.

End point type	Secondary
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End point timeframe:

Baseline to Day 84 (Week 12)

End point values	LMB763 100 mg	LMB763 50 mg	Pooled Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10 ^[34]	17 ^[35]	18 ^[36]	
Units: kilopascal (kPa)				
geometric mean (geometric coefficient of variation)				
Baseline for Day 84 Analysis	7.689 (± 71.1)	6.082 (± 29.5)	7.108 (± 52.5)	
Change from Baseline at Day 84	0.955 (± 35.3)	1.053 (± 26.9)	1.041 (± 38.6)	

Notes:

[34] - PD analysis set: n = 7, 7

[35] - PD analysis set: n = 15, 15

[36] - PD analysis set: n = 16, 16

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Enhanced Liver Fibrosis (ELF) Test Panel

End point title	Change From Baseline in Enhanced Liver Fibrosis (ELF) Test Panel
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End point description:

Enhanced liver fibrosis test (ELF) panel included hyaluronic acid (HA), tissue inhibitor of metalloproteinases (TIMP-1), and amino-terminal pro-peptide of procollagen type III (PIIINP) as markers of liver fibrosis. Baseline was defined as the last available measurement prior to the first dose. Geometric Mean and Geometric Coefficient of Variation for change are based on log-transformed ratio to baseline (i.e., change from baseline in the log domain). PD analysis set included all subjects with available PD data and no protocol deviations with relevant impact on PD data. 'n' represents the number of subjects in each category with a value at both Baseline and that time point.

End point type	Secondary
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End point timeframe:

Baseline to Days 42 and 84

End point values	LMB763 100 mg	LMB763 50 mg	Pooled Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37 ^[37]	44 ^[38]	40 ^[39]	
Units: ELF score				
geometric mean (geometric coefficient of variation)				
Baseline for Day 42 Analysis	9.063 (± 7.3)	8.731 (± 8.2)	9.212 (± 8.0)	
Change from Baseline at Day 42	1.005 (± 5.5)	1.016 (± 5.8)	1.009 (± 7.5)	
Baseline for Day 84 Analysis	9.051 (± 7.7)	8.739 (± 8.4)	9.220 (± 7.8)	
Change from Baseline at Day 84	1.005 (± 5.9)	1.030 (± 6.2)	1.007 (± 6.3)	

Notes:

[37] - PD analysis set. n = 26, 26, 24, 24

[38] - PD analysis set. n = 42, 42, 37, 37

[39] - PD analysis set. n = 33, 33, 33, 33

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Fibrosis Biomarker Test

End point title	Change From Baseline in Fibrosis Biomarker Test
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End point description:

Fibrosis Biomarker test included hyaluronic acid (HA), amino-terminal pro-peptide of procollagen type III (PIIINP), and tissue inhibitor of metalloproteinases (TIMP-1) as markers of liver fibrosis. Baseline was defined as the last available measurement prior to the first dose. Geometric Mean and Geometric Coefficient of Variation for change are based on log-transformed ratio to baseline (i.e., change from baseline in the log domain). PD analysis set included all subjects with available PD data and no protocol deviations with relevant impact on PD data. 'n' represents the number of subjects in each category with a value at both Baseline and that time point.

End point type	Secondary
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End point timeframe:

Baseline to Days 42 and 84

End point values	LMB763 100 mg	LMB763 50 mg	Pooled Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37 ^[40]	44 ^[41]	40 ^[42]	
Units: micrograms per litre (ug/L)				
geometric mean (geometric coefficient of variation)				
HA: Baseline for Day 42 Analysis	33.646 (± 72.2)	26.869 (± 75.4)	39.282 (± 74.9)	
HA: Change from Baseline at Day 42	1.002 (± 49.5)	1.133 (± 54.4)	1.111 (± 77.0)	
HA: Baseline for Day 84 Analysis	32.246 (± 72.9)	27.320 (± 78.2)	40.865 (± 79.5)	
HA: Change from Baseline at Day 84	1.023 (± 54.0)	1.254 (± 51.4)	1.071 (± 64.9)	
PIIINP: Baseline for Day 42 Analysis	9.023 (± 31.3)	7.850 (± 28.2)	9.087 (± 35.5)	
PIIINP: Change from Baseline at Day 42	1.016 (± 22.8)	1.071 (± 24.3)	1.010 (± 26.4)	
PIIINP: Baseline for Day 84 Analysis	9.263 (± 34.6)	7.859 (± 27.4)	8.934 (± 32.3)	
PIIINP: Change from Baseline at Day 84	1.003 (± 21.2)	1.048 (± 26.9)	1.004 (± 20.1)	
TIMP-1: Baseline for Day 42 Analysis	242.99 (± 17.5)	199.21 (± 78.4)	254.37 (± 23.1)	
TIMP-1: Change from Baseline at Day 42	1.060 (± 14.6)	1.017 (± 11.9)	0.995 (± 13.3)	
TIMP-1: Baseline for Day 84 Analysis	247.42 (± 18.8)	193.32 (± 83.6)	245.09 (± 20.5)	
TIMP-1: Change from Baseline at Day 84	1.073 (± 17.0)	1.036 (± 10.4)	1.000 (± 19.2)	

Notes:

[40] - PD analysis set. n = 26, 26, 24, 24, 26, 26, 24, 24, 26, 26, 24, 24

[41] - PD analysis set. n = 43, 43, 38, 38, 43, 43, 38, 38, 43, 43, 38, 38

[42] - PD analysis set. n = 33, 33, 33, 33, 33, 33, 33, 33, 33, 33, 33, 33

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Fasting Lipid Profile: Cholesterol (Chol) and Triglycerides (TG)

End point title	Change From Baseline in Fasting Lipid Profile: Cholesterol (Chol) and Triglycerides (TG)
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End point description:

Lipid measurements were collected under fasted conditions. Baseline was defined as the last available measurement prior to the first dose. Geometric Mean and Geometric Coefficient of Variation for change are based on log-transformed ratio to baseline (i.e., change from baseline in the log domain). PD analysis set included all subjects with available PD data and no protocol deviations with relevant impact on PD data. 'n' represents the number of subjects in each category with a value at both Baseline and that time point.

End point type	Secondary
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End point timeframe:

Baseline to Days 7, 14, 28, 42, 56, 84 and 112 (EOS)

End point values	LMB763 100 mg	LMB763 50 mg	Pooled Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37 ^[43]	44 ^[44]	40 ^[45]	
Units: milligrams per decilitre (mg/dL)				
geometric mean (geometric coefficient of variation)				
Chol: Baseline for Day 7 Analysis	184.85 (± 23.0)	183.30 (± 22.1)	188.97 (± 22.0)	
Chol: Change from Baseline at Day 7	0.957 (± 14.5)	1.001 (± 9.0)	1.002 (± 10.2)	
Chol: Baseline for Day 14 Analysis	186.57 (± 23.1)	183.30 (± 22.1)	188.97 (± 22.0)	
Chol: Change from Baseline at Day 14	0.963 (± 17.0)	1.037 (± 11.8)	1.000 (± 10.4)	
Chol: Baseline for Day 28 Analysis	188.09 (± 23.2)	183.50 (± 22.3)	190.44 (± 22.4)	
Chol: Change from Baseline at Day 28	0.952 (± 15.2)	1.025 (± 14.6)	1.007 (± 12.2)	
Chol: Baseline for Day 42 Analysis	206.50 (± 18.3)	182.59 (± 22.3)	191.65 (± 21.1)	
Chol: Change from Baseline at Day 42	0.943 (± 17.2)	1.001 (± 15.1)	0.940 (± 14.2)	
Chol: Baseline for Day 56 Analysis	192.25 (± 22.5)	182.39 (± 22.5)	190.33 (± 21.0)	
Chol: Change from Baseline at Day 56	0.963 (± 17.2)	1.033 (± 16.1)	1.002 (± 15.2)	
Chol: Baseline for Day 84 Analysis	188.88 (± 22.0)	181.63 (± 22.4)	187.20 (± 23.6)	
Chol: Change from Baseline at Day 84	0.958 (± 17.9)	1.037 (± 18.9)	1.006 (± 13.5)	
Chol: Baseline for Day 112 (EOS) Analysis	187.34 (± 22.8)	181.47 (± 22.0)	187.13 (± 23.1)	

Chol: Change from Baseline at Day 112 (EOS)	0.989 (± 13.6)	1.039 (± 16.8)	1.009 (± 13.2)
TG: Baseline for Day 7 Analysis	185.66 (± 55.0)	198.88 (± 47.8)	175.18 (± 58.7)
TG: Change from Baseline at Day 7	0.876 (± 38.8)	0.854 (± 25.8)	1.020 (± 28.6)
TG: Baseline for Day 14 Analysis	178.22 (± 50.5)	198.88 (± 47.8)	175.18 (± 58.7)
TG: Change from Baseline at Day 14	0.864 (± 36.2)	0.881 (± 28.1)	1.013 (± 35.9)
TG: Baseline for Day 28 Analysis	166.54 (± 45.0)	201.00 (± 47.7)	177.66 (± 60.6)
TG: Change from Baseline at Day 28	0.968 (± 36.4)	0.937 (± 37.0)	0.971 (± 33.7)
TG: Baseline for Day 42 Analysis	181.97 (± 44.6)	203.65 (± 47.4)	174.48 (± 64.4)
TG: Change from Baseline at Day 42	0.868 (± 34.5)	0.872 (± 36.1)	0.920 (± 35.2)
TG: Baseline for Day 56 Analysis	167.66 (± 47.5)	202.64 (± 48.8)	174.78 (± 60.6)
TG: Change from Baseline at Day 56	0.932 (± 34.2)	0.948 (± 38.9)	0.965 (± 28.1)
TG: Baseline for Day 84 Analysis	163.71 (± 48.6)	201.96 (± 49.5)	184.99 (± 59.7)
TG: Change from Baseline at Day 84	0.863 (± 43.8)	0.956 (± 45.8)	0.947 (± 33.3)
TG: Baseline for Day 112 (EOS) Analysis	172.80 (± 46.1)	203.55 (± 49.2)	179.36 (± 62.5)
TG: Change from Baseline at Day 112 (EOS)	0.931 (± 38.5)	1.003 (± 39.9)	1.039 (± 39.0)

Notes:

[43] - PD analysis: n=36,

36,34,34,29,29,19,19,25,25,24,24,22,22,36,36,34,34,29,29,19,19,25,25,24,24,22,22

[44] - PD analysis: n=44,

44,44,44,43,43,42,42,41,41,40,40,39,39,44,44,44,44,43,43,42,42,41,41,40,40, 39,39

[45] - PD analysis: n=40,

40,40,40,37,37,30,30,33,33,32,32,33,33,40,40,40,40,37,37,30,30,33,33,32,32,33,33

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Fasting Lipid Profile: High-density Lipoprotein (HDL) and Low-density Lipoprotein (LDL) Cholesterol

End point title	Change From Baseline in Fasting Lipid Profile: High-density Lipoprotein (HDL) and Low-density Lipoprotein (LDL) Cholesterol
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End point description:

Baseline was defined as the last available measurement prior to the first dose. Geometric Mean and Geometric Coefficient of Variation for change are based on log-transformed ratio to baseline (i.e., change from baseline in the log domain). PD analysis set included all subjects with available PD data and no protocol deviations with relevant impact on PD data. 'n' represents the number of subjects in each category with a value at both Baseline and that time point.

End point type	Secondary
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End point timeframe:

Baseline to Days 7, 14, 28, 42, 56, 84 and 112 (EOS)

End point values	LMB763 100 mg	LMB763 50 mg	Pooled Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37 ^[46]	44 ^[47]	40 ^[48]	
Units: millimole per litre (mmol/L)				
geometric mean (geometric coefficient of variation)				
HDL: Baseline for Day 7 Analysis	1.059 (± 30.0)	1.014 (± 25.4)	1.206 (± 28.2)	
HDL: Change from Baseline at Day 7	0.874 (± 15.0)	0.969 (± 10.0)	1.017 (± 12.7)	
HDL: Baseline for Day 14 Analysis	1.093 (± 24.8)	1.014 (± 25.4)	1.206 (± 28.2)	
HDL: Change from Baseline at Day 14	0.876 (± 19.1)	0.982 (± 13.4)	0.979 (± 10.0)	
HDL: Baseline for Day 28 Analysis	1.143 (± 23.8)	1.014 (± 25.7)	1.221 (± 28.9)	
HDL: Change from Baseline at Day 28	0.862 (± 14.1)	0.952 (± 15.1)	1.009 (± 14.7)	
HDL: Baseline for Day 42 Analysis	1.172 (± 26.9)	1.007 (± 25.7)	1.212 (± 30.6)	
HDL: Change from Baseline at Day 42	0.888 (± 19.4)	0.941 (± 15.5)	1.005 (± 12.2)	
HDL: Baseline for Day 56 Analysis	1.148 (± 25.5)	1.008 (± 25.9)	1.226 (± 29.1)	
HDL: Change from Baseline at Day 56	0.875 (± 17.0)	0.956 (± 15.1)	1.022 (± 13.9)	
HDL: Baseline for Day 84 Analysis	1.158 (± 24.9)	1.016 (± 26.6)	1.219 (± 29.7)	
HDL: Change from Baseline at Day 84	0.891 (± 16.1)	0.920 (± 19.9)	1.031 (± 12.5)	
HDL: Baseline for Day 112 (EOS) Analysis	1.115 (± 22.1)	1.013 (± 26.1)	1.218 (± 29.6)	
HDL: Change from Baseline at Day 112 (EOS)	1.004 (± 14.5)	1.037 (± 17.2)	1.007 (± 11.5)	
LDL: Baseline for Day 7 Analysis	2.647 (± 39.0)	2.591 (± 40.6)	2.628 (± 34.2)	
LDL: Change from Baseline at Day 7	1.009 (± 18.7)	1.076 (± 20.2)	0.977 (± 17.1)	
LDL: Baseline for Day 14 Analysis	2.664 (± 39.8)	2.591 (± 40.6)	2.666 (± 34.3)	
LDL: Change from Baseline at Day 14	1.021 (± 23.6)	1.125 (± 19.7)	0.998 (± 14.3)	
LDL: Baseline for Day 28 Analysis	2.612 (± 39.4)	2.553 (± 40.7)	2.614 (± 36.3)	
LDL: Change from Baseline at Day 28	0.996 (± 27.5)	1.092 (± 23.0)	1.017 (± 15.7)	
LDL: Baseline for Day 42 Analysis	3.070 (± 28.7)	2.559 (± 41.0)	2.679 (± 35.1)	
LDL: Change from Baseline at Day 42	0.989 (± 29.9)	1.079 (± 24.5)	0.914 (± 21.1)	
LDL: Baseline for Day 56 Analysis	2.841 (± 32.0)	2.527 (± 42.0)	2.621 (± 36.0)	
LDL: Change from Baseline at Day 56	1.011 (± 27.9)	1.091 (± 24.8)	0.991 (± 24.7)	
LDL: Baseline for Day 84 Analysis	2.725 (± 30.8)	2.528 (± 41.8)	2.498 (± 36.8)	
LDL: Change from Baseline at Day 84	1.029 (± 22.5)	1.107 (± 31.7)	1.025 (± 22.2)	
LDL: Baseline for Day 112 (EOS) Analysis	2.695 (± 31.6)	2.418 (± 40.0)	2.482 (± 36.2)	
LDL: Change from Baseline at Day 112 (EOS)	1.010 (± 18.7)	1.035 (± 34.1)	1.026 (± 19.9)	

Notes:

[46] - PD analysis: n=36,
36,34,34,29,29,19,19,24,24,24,24,22,22,34,34,33,33,29,29,19,19,24,24,24,24,22,22
[47] - PD analysis: n=44,
44,44,44,43,43,42,42,41,41,40,40,39,39,43,43,43,43,41,41,41,41,38,38,38,38,35,35
[48] - PD analysis: n=40,
40,40,40,37,37,30,30,33,33,32,32,33,33,37,37,35,35,36,36,28,28,32,32,29,29,29,29

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Visual Analog Scale (VAS) for Itching of Skin

End point title	Change From Baseline in Visual Analog Scale (VAS) for Itching of Skin
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End point description:

A 10 cm VAS was used to assess the severity of subjects itch (ranging from 0 = no itch at all to 10 =

the worst imaginable itch). The score (distance from left) on the VAS was recorded by the subject marking with a line and used to test for an effect of LMB763 over placebo. Baseline was defined as the last available measurement prior to the first dose. A positive change from Baseline indicates improvement. PD analysis set included all subjects with available PD data and no protocol deviations with relevant impact on PD data. 'n' represents the number of subjects in each category with a value at both Baseline and that time point.

End point type	Secondary
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End point timeframe:

Baseline to Day 84 (Week 12)

End point values	LMB763 100 mg	LMB763 50 mg	Pooled Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	37 ^[49]	44 ^[50]	40 ^[51]	
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline for Day 84 Analysis	8.87 (± 19.108)	4.62 (± 10.356)	9.68 (± 19.552)	
Change from Baseline at Day 84	9.35 (± 18.746)	4.85 (± 21.798)	2.03 (± 24.037)	

Notes:

[49] - PD analysis set: n = 23, 23

[50] - PD analysis set: n = 39, 39

[51] - PD analysis set: n = 34, 34

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were 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 LPLV (up to Day 112 (EOS)).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	LMB763 100 mg
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Reporting group description:

LMB763 100 mg

Reporting group title	LMB763 50 mg
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Reporting group description:

LMB763 50 mg

Reporting group title	Pooled Placebo
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Reporting group description:

Pooled Placebo

Serious adverse events	LMB763 100 mg	LMB763 50 mg	Pooled Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 37 (5.41%)	3 / 44 (6.82%)	0 / 40 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign small intestinal neoplasm			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (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
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice cholestatic			

subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Otitis media			
subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	LMB763 100 mg	LMB763 50 mg	Pooled Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 37 (94.59%)	37 / 44 (84.09%)	33 / 40 (82.50%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign breast neoplasm			
subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Lipoma			
subjects affected / exposed	0 / 37 (0.00%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 37 (0.00%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Hypertension			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	1	0	1
Hypotension			

subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1	0 / 44 (0.00%) 0	0 / 40 (0.00%) 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Discomfort			
subjects affected / exposed	0 / 37 (0.00%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	2 / 37 (5.41%)	2 / 44 (4.55%)	4 / 40 (10.00%)
occurrences (all)	2	2	4
Feeling cold			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Influenza like illness			
subjects affected / exposed	4 / 37 (10.81%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	4	0	0
Peripheral swelling			
subjects affected / exposed	0 / 37 (0.00%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Seasonal allergy			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Ovarian calcification			
subjects affected / exposed	0 / 37 (0.00%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Vaginal haemorrhage			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal			

disorders			
Bronchial hyperreactivity			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Cough			
subjects affected / exposed	3 / 37 (8.11%)	2 / 44 (4.55%)	2 / 40 (5.00%)
occurrences (all)	4	3	2
Dyspnoea			
subjects affected / exposed	0 / 37 (0.00%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Epistaxis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Nasal congestion			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Paranasal sinus discomfort			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Respiratory tract congestion			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Rhinitis allergic			
subjects affected / exposed	0 / 37 (0.00%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Sinus congestion			
subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Sneezing			

subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1	0 / 44 (0.00%) 0	0 / 40 (0.00%) 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	3 / 40 (7.50%)
occurrences (all)	0	1	3
Insomnia			
subjects affected / exposed	2 / 37 (5.41%)	2 / 44 (4.55%)	0 / 40 (0.00%)
occurrences (all)	2	2	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 37 (2.70%)	2 / 44 (4.55%)	4 / 40 (10.00%)
occurrences (all)	1	2	4
Albumin urine present			
subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Alpha-2 macroglobulin			
subjects affected / exposed	0 / 37 (0.00%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Alpha-2 macroglobulin increased			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Apolipoprotein A-I decreased			
subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 37 (10.81%)	1 / 44 (2.27%)	1 / 40 (2.50%)
occurrences (all)	4	1	1
Bacterial test positive			
subjects affected / exposed	0 / 37 (0.00%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Basophil count increased			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	2	0	0
Blood alkaline phosphatase increased			

subjects affected / exposed	3 / 37 (8.11%)	1 / 44 (2.27%)	0 / 40 (0.00%)
occurrences (all)	3	1	0
Blood bilirubin increased			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Blood calcium decreased			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 37 (0.00%)	0 / 44 (0.00%)	3 / 40 (7.50%)
occurrences (all)	0	0	3
Blood creatinine increased			
subjects affected / exposed	3 / 37 (8.11%)	1 / 44 (2.27%)	0 / 40 (0.00%)
occurrences (all)	3	1	0
Blood glucose increased			
subjects affected / exposed	1 / 37 (2.70%)	1 / 44 (2.27%)	2 / 40 (5.00%)
occurrences (all)	1	1	2
Blood triglycerides increased			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Blood urea increased			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Blood urine present			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
C-reactive protein increased			
subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Crystal urine present			
subjects affected / exposed	0 / 37 (0.00%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	2
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	1	0	1

Electrocardiogram abnormal subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1	0 / 44 (0.00%) 0	0 / 40 (0.00%) 0
Eosinophil count increased subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	0 / 44 (0.00%) 0	2 / 40 (5.00%) 2
Free fatty acids increased subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1	1 / 44 (2.27%) 1	0 / 40 (0.00%) 0
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1	0 / 44 (0.00%) 0	2 / 40 (5.00%) 2
Glomerular filtration rate decreased subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1	0 / 44 (0.00%) 0	0 / 40 (0.00%) 0
Glycosylated haemoglobin increased subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	0 / 44 (0.00%) 0	1 / 40 (2.50%) 1
Low density lipoprotein decreased subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1	0 / 44 (0.00%) 0	0 / 40 (0.00%) 0
Lymphocyte count decreased subjects affected / exposed occurrences (all)	3 / 37 (8.11%) 3	0 / 44 (0.00%) 0	0 / 40 (0.00%) 0
Lymphocyte count increased subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2	0 / 44 (0.00%) 0	2 / 40 (5.00%) 2
Neutrophil count decreased subjects affected / exposed occurrences (all)	4 / 37 (10.81%) 6	1 / 44 (2.27%) 1	4 / 40 (10.00%) 4
Prothrombin time prolonged subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1	0 / 44 (0.00%) 0	0 / 40 (0.00%) 0
Transaminases increased			

subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Urine albumin/creatinine ratio			
subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Urine albumin/creatinine ratio increased			
subjects affected / exposed	2 / 37 (5.41%)	4 / 44 (9.09%)	5 / 40 (12.50%)
occurrences (all)	3	4	5
Urine protein/creatinine ratio increased			
subjects affected / exposed	7 / 37 (18.92%)	8 / 44 (18.18%)	3 / 40 (7.50%)
occurrences (all)	10	8	3
White blood cell count decreased			
subjects affected / exposed	1 / 37 (2.70%)	1 / 44 (2.27%)	0 / 40 (0.00%)
occurrences (all)	1	1	0
White blood cell count increased			
subjects affected / exposed	0 / 37 (0.00%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
White blood cells urine positive			
subjects affected / exposed	0 / 37 (0.00%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Burns second degree			
subjects affected / exposed	0 / 37 (0.00%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Contusion			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	2 / 40 (5.00%)
occurrences (all)	1	0	2
Fall			
subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Ligament sprain			

subjects affected / exposed	0 / 37 (0.00%)	2 / 44 (4.55%)	1 / 40 (2.50%)
occurrences (all)	0	2	1
Muscle strain			
subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Skin abrasion			
subjects affected / exposed	1 / 37 (2.70%)	1 / 44 (2.27%)	0 / 40 (0.00%)
occurrences (all)	1	1	0
Wrist fracture			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 37 (0.00%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Nervous system disorders			
Diabetic neuropathy			
subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Dizziness			
subjects affected / exposed	0 / 37 (0.00%)	3 / 44 (6.82%)	1 / 40 (2.50%)
occurrences (all)	0	3	1
Head discomfort			
subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	3 / 37 (8.11%)	7 / 44 (15.91%)	8 / 40 (20.00%)
occurrences (all)	3	8	9
Lumbar radiculopathy			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Migraine			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	1	0	1
Myasthenia gravis			

subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	1 / 37 (2.70%)	3 / 44 (6.82%)	0 / 40 (0.00%)
occurrences (all)	1	3	0
Presyncope			
subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Sciatica			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	1	0	1
Somnolence			
subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Syncope			
subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Motion sickness			
subjects affected / exposed	0 / 37 (0.00%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Vertigo			
subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Blepharitis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			

Abdominal discomfort			
subjects affected / exposed	1 / 37 (2.70%)	1 / 44 (2.27%)	1 / 40 (2.50%)
occurrences (all)	1	1	1
Abdominal distension			
subjects affected / exposed	0 / 37 (0.00%)	2 / 44 (4.55%)	2 / 40 (5.00%)
occurrences (all)	0	2	2
Abdominal pain			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	3 / 40 (7.50%)
occurrences (all)	1	0	3
Abdominal pain upper			
subjects affected / exposed	3 / 37 (8.11%)	2 / 44 (4.55%)	3 / 40 (7.50%)
occurrences (all)	3	2	3
Abnormal faeces			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	4 / 37 (10.81%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	4	0	0
Diarrhoea			
subjects affected / exposed	4 / 37 (10.81%)	4 / 44 (9.09%)	4 / 40 (10.00%)
occurrences (all)	6	4	7
Dyspepsia			
subjects affected / exposed	2 / 37 (5.41%)	0 / 44 (0.00%)	3 / 40 (7.50%)
occurrences (all)	3	0	3
Faeces pale			
subjects affected / exposed	2 / 37 (5.41%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	2	0	0
Flatulence			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	0 / 40 (0.00%)
occurrences (all)	0	1	0

Hyperchlorhydria			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	1	0	1
Melaena			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	7 / 37 (18.92%)	5 / 44 (11.36%)	2 / 40 (5.00%)
occurrences (all)	7	6	3
Tongue pruritus			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	1 / 37 (2.70%)	3 / 44 (6.82%)	0 / 40 (0.00%)
occurrences (all)	1	3	0
Hepatobiliary disorders			
Jaundice			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Blister			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Dermal cyst			
subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Dermatitis contact			
subjects affected / exposed	0 / 37 (0.00%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Dry skin			
subjects affected / exposed	0 / 37 (0.00%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Ecchymosis			

subjects affected / exposed	1 / 37 (2.70%)	1 / 44 (2.27%)	0 / 40 (0.00%)
occurrences (all)	1	1	0
Erythema			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	1	0	1
Hyperhidrosis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Petechiae			
subjects affected / exposed	0 / 37 (0.00%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	20 / 37 (54.05%)	13 / 44 (29.55%)	6 / 40 (15.00%)
occurrences (all)	28	14	6
Pruritus generalised			
subjects affected / exposed	2 / 37 (5.41%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	2	0	0
Psoriasis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	0 / 37 (0.00%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Rash erythematous			
subjects affected / exposed	2 / 37 (5.41%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	2	0	0
Rash follicular			
subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Rash maculo-papular			
subjects affected / exposed	0 / 37 (0.00%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Rash pruritic			
subjects affected / exposed	4 / 37 (10.81%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	4	0	0
Skin atrophy			

subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Skin mass			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Pollakiuria			
subjects affected / exposed	0 / 37 (0.00%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Proteinuria			
subjects affected / exposed	0 / 37 (0.00%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Renal disorder			
subjects affected / exposed	0 / 37 (0.00%)	4 / 44 (9.09%)	1 / 40 (2.50%)
occurrences (all)	0	4	1
Urine abnormality			
subjects affected / exposed	0 / 37 (0.00%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Urine odour abnormal			
subjects affected / exposed	0 / 37 (0.00%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 37 (0.00%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Back pain			
subjects affected / exposed	1 / 37 (2.70%)	3 / 44 (6.82%)	1 / 40 (2.50%)
occurrences (all)	1	3	1
Bursitis			
subjects affected / exposed	0 / 37 (0.00%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Muscle spasms			

subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	1 / 40 (2.50%)
occurrences (all)	0	1	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 37 (0.00%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	0 / 37 (0.00%)	0 / 44 (0.00%)	3 / 40 (7.50%)
occurrences (all)	0	0	3
Musculoskeletal stiffness			
subjects affected / exposed	0 / 37 (0.00%)	0 / 44 (0.00%)	1 / 40 (2.50%)
occurrences (all)	0	0	1
Neck pain			
subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	1 / 40 (2.50%)
occurrences (all)	0	1	1
Pain in extremity			
subjects affected / exposed	0 / 37 (0.00%)	2 / 44 (4.55%)	3 / 40 (7.50%)
occurrences (all)	0	3	4
Infections and infestations			
Atypical pneumonia			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Bronchitis			
subjects affected / exposed	1 / 37 (2.70%)	1 / 44 (2.27%)	0 / 40 (0.00%)
occurrences (all)	1	1	0
Ear infection			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Folliculitis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Influenza			
subjects affected / exposed	1 / 37 (2.70%)	1 / 44 (2.27%)	4 / 40 (10.00%)
occurrences (all)	1	1	4
Nail infection			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0

Nasopharyngitis			
subjects affected / exposed	1 / 37 (2.70%)	2 / 44 (4.55%)	3 / 40 (7.50%)
occurrences (all)	2	2	3
Oral herpes			
subjects affected / exposed	2 / 37 (5.41%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	2	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 37 (0.00%)	2 / 44 (4.55%)	0 / 40 (0.00%)
occurrences (all)	0	2	0
Rhinitis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	2 / 37 (5.41%)	2 / 44 (4.55%)	0 / 40 (0.00%)
occurrences (all)	2	2	0
Tinea infection			
subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Tooth abscess			
subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 37 (5.41%)	4 / 44 (9.09%)	2 / 40 (5.00%)
occurrences (all)	3	4	2
Urinary tract infection			
subjects affected / exposed	0 / 37 (0.00%)	2 / 44 (4.55%)	3 / 40 (7.50%)
occurrences (all)	0	2	3
Viral infection			
subjects affected / exposed	0 / 37 (0.00%)	4 / 44 (9.09%)	1 / 40 (2.50%)
occurrences (all)	0	4	2
Viral myositis			
subjects affected / exposed	0 / 37 (0.00%)	1 / 44 (2.27%)	0 / 40 (0.00%)
occurrences (all)	0	1	0
Viral rhinitis			
subjects affected / exposed	1 / 37 (2.70%)	0 / 44 (0.00%)	0 / 40 (0.00%)
occurrences (all)	1	0	0

Vulvovaginal candidiasis subjects affected / exposed occurrences (all)	1 / 37 (2.70%) 1	0 / 44 (0.00%) 0	0 / 40 (0.00%) 0
Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	1 / 44 (2.27%) 2	0 / 40 (0.00%) 0
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 2	0 / 44 (0.00%) 0	0 / 40 (0.00%) 0
Gout subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	1 / 44 (2.27%) 1	0 / 40 (0.00%) 0
Hypercholesterolaemia subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	1 / 44 (2.27%) 1	0 / 40 (0.00%) 0
Hyperglycaemia subjects affected / exposed occurrences (all)	4 / 37 (10.81%) 4	4 / 44 (9.09%) 6	0 / 40 (0.00%) 0
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	3 / 44 (6.82%) 4	0 / 40 (0.00%) 0
Hypoglycaemia subjects affected / exposed occurrences (all)	2 / 37 (5.41%) 3	0 / 44 (0.00%) 0	0 / 40 (0.00%) 0
Type 2 diabetes mellitus subjects affected / exposed occurrences (all)	0 / 37 (0.00%) 0	2 / 44 (4.55%) 2	0 / 40 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 January 2017	Amendment 1 was generated in response to requests from the Medicines and Healthcare Products Regulatory Agency (MHRA) to include an additional pregnancy test and add serum phosphate to the clinical chemistry panel in accordance with the recommended renal monitoring procedures in the Investigator Brochure.
01 May 2017	Based on US FDA feedback regarding the potent inhibitory effects of nidufexor on CYP2C8 ($K_i = 0.0213 \mu\text{M}$, $\text{IC}_{50} = 0.41 \mu\text{M}$), which suggested a potential for drug-drug interactions (DDI) to occur between CYP2C8 substrates and nidufexor, the protocol was amended to highlight the potential for DDI and emphasize the potential for nidufexor to increase exposure of drugs metabolized by CYP2C8, including repaglinide, pioglitazone and rosiglitazone, and those dependent on export by BCRP. For all these drugs careful attention was paid to the drug interaction sections of the prescribing information.
01 October 2017	Amendment v03 aimed to explore a reduced dose of nidufexor which was expected to have a pharmacological effect on biomarkers of disease activity, as well as to lower the ALT threshold required for inclusion based on emerging data on the NASH phenotype and requirements for Phase 2 studies, and feedback received from investigators.

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.

The sponsor decided to terminate the study early, as data obtained were deemed sufficient to inform any potential future development steps; interim results showed that the 50 mg nidufexor dose was well tolerated with favourable efficacy.

Notes: