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Novartis Clinical Trial Results

Sponsor

Novartis

Generic Drug Name

Nidufexor (LMB763)

Trial Indication(s)

Patients with non-alcoholic steatohepatitis (NASH)

Protocol Number

CLMB763X2201

Protocol Title

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)

Clinical Trial Phase

Phase II

Phase of Drug Development

Phase II

Study Start/End Dates

24-Oct-2016 to 04-Mar-2019

Reason for Termination

Following interim analysis 3, Novartis decided to terminate the study early, as data obtained were deemed sufficient to inform any potential future development steps. The interim results showed that the 50 mg nidufexor dose is well tolerated with favourable efficacy based on ALT and liver fat reduction.

Study Design/Methodology

This was a non-confirmatory, multicenter, patient and investigator blinded, randomized, placebo-controlled, parallel group, two cohort study in patients with NASH. The sponsor was allowed to be unblinded to the treatment assignment of all patients to facilitate continuous safety monitoring.
The study was conducted in two cohorts:
Cohort 1: Approximately 96 patients were planned to be randomized in a 2:1 ratio to receive nidufexor 100 mg or matching placebo (in line with the study design outlined in protocol amendment v02 dated 17 May 2017). Upon implementation of protocol amendment v03 (see below), all patients enrolled into this cohort had to complete the study at that dose, but no further patients were recruited into Cohort 1.
Cohort 2: Protocol Amendment v03 had been instituted to assess a lower dose of 50 mg nidufexor. An additional approximately 96 patients were planned to be randomized in a 2:1 ratio to receive nidufexor 50 mg or placebo to ensure ~81 completers in this cohort.

Centers

25 centers in 6 countries: Australia (1), Switzerland (3), United Kingdom (1), Jordan (1), New Zealand (4), United States (15)

Objectives:

Primary objective(s)

Primary Objective:

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

Secondary objective(s)

- To evaluate the pharmacokinetics (PK) of nidufexor in NASH patients.
- To determine the effect of nidufexor on intrahepatic lipid after 12 weeks of treatment.
- To determine the effect of nidufexor on anthropometric assessments after 12 weeks of treatment.
- To determine the effect of nidufexor on non-invasive markers of liver fibrosis.

Test Product (s), Dose(s), and Mode(s) of Administration

Study medication was self-administered by the patient orally once daily 12 weeks (84 days).

Patients in each cohort were assigned to one of the following two treatments in a ratio of 2:1. Study treatments are defined as:

Cohort 1:

- LMB763 100 mg (1 × LMB763 100 mg capsule)
- Matching placebo (1 × Matching placebo capsule)

Cohort 2:

- LMB763 50 mg (2 × LMB763 25 mg capsules)
- Matching placebo (× Matching placebo capsules)

Statistical Methods

For all analysis sets, patients were analyzed according to the study treatment received. All placebo subjects were pooled. Subjects with dose frequency/dose change due to AE were analyzed according to the treatment received up to the dose frequency/dose change.

The safety analysis set included all patients that received any study drug.

The PK analysis set included all patients 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.

The PD analysis set included all patients with available PD data and no protocol deviations with relevant impact on PD data

For the End of Study (EOS) visit only data from study completers were included in the summary/analysis tables/figures.

All data for background and demographic variables were listed by treatment group and patient. Summary statistics were provided by treatment group.

Relevant medical history, current medical conditions, results of laboratory screens and any other relevant information were listed by treatment group and patient.
Data for study drug administration and concomitant therapies were listed by treatment group and patient.
The primary objective of this study was to assess the safety and tolerability of nidufexor as well as the efficacy of nidufexor on ALT in NASH patients during 12 weeks of treatment. Safety/tolerability data were summarized.
One of the primary objectives of this study was to assess the efficacy of nidufexor in NASH patients during 12 weeks of treatment. Change from baseline to Week 12 in ALT was the primary efficacy variable. 'Baseline' was defined as the mean of ALT levels at baseline (V2) and pre-dose (V101) visits.
The absolute and change from baseline as well as percent change from baseline ALT measurements were listed by treatment, patient and visit/time and descriptive statistics were provided by treatment and visit/time. Summary statistics included mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum as appropriate.
Mean (SE) absolute and change from baseline ALT as well as geometric mean ratio to baseline ALT (90% CI) over time were plotted by treatment.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Male/female patients, 18 years or older
- Written informed consent
- Presence of NASH by histologic evidence (liver biopsy) and elevated alanine aminotransferase (ALT), OR phenotypic diagnosis of NASH based on elevated ALT, BMI and diagnosis of Type 2 diabetes mellitus

Exclusion Criteria:

- Current use of obeticholic acid (OCA)
- New initiation GLP-1 agonists such as liraglutide, exenatide , lixisenatide, albiglutide or dulaglutide within 3 months of screening
- Pregnant or nursing (lactating) women
- Women of child-bearing potential, unless they are using highly effective methods of contraception during dosing and for 5 days after stopping study medication
- Current or history of significant alcohol consumption for a period of more than 3 consecutive months within 1 year prior to screening
- Clinical evidence of hepatic decompensation or severe liver impairment

- Previous diagnosis of other forms of chronic liver disease
- Uncontrolled diabetes mellitus
- History or current diagnosis of ECG abnormalities
- Patients with contraindications to MRI imaging

Participant Flow Table

Subject disposition - n (percent) of subjects - All subjects

	LMB763			
	100 mg N=37 n (%)	50 mg N=44 n (%)	Pooled placebo N=40 n (%)	Total N=121 n (%)
Subjects				
Completed	22 (59.5)	39 (88.6)	33 (82.5)	94 (77.7)
Discontinued	15 (40.5)	5 (11.4)	7 (17.5)	27 (22.3)
Main cause of discontinuation				
Adverse Event	11 (29.7)	-	4 (10.0)	15 (12.4)
Non-Compliance With Study Drug	-	-	1 (2.5)	1 (0.8)
Other	3 (8.1)	1 (2.3)	1 (2.5)	5 (4.1)
Physician Decision	1 (2.7)	1 (2.3)	-	2 (1.7)
Withdrawal By Subject	-	3 (6.8)	1 (2.5)	4 (3.3)

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Baseline Characteristics

Subject demographics by treatment group - Safety analysis set

		LMB763			
		100 mg N=37	50 mg N=44	Pooled placebo N=40	Total N=121
Age (years)	Mean (SD)	51.3 (15.55)	49.5 (8.45)	51.6 (11.65)	50.8 (11.96)
	Median	53.0	49.0	54.0	53.0
	Range	22 - 75	32 - 63	18 - 67	18 - 75
Sex - n(%)	Female	22 (59%)	23 (52%)	24 (60%)	69 (57%)
	Male	15 (41%)	21 (48%)	16 (40%)	52 (43%)
Race - n(%)	Asian	2 (5%)	3 (7%)	4 (10%)	9 (7%)
	Black Or African American	1 (3%)	2 (5%)		3 (2%)
	Multiple	1 (3%)	1 (2%)	3 (8%)	5 (4%)
	Native Hawaiian Or Other Pacific Islander	1 (3%)		1 (3%)	2 (2%)
	White	32 (86%)	37 (84%)	31 (78%)	100 (83%)
	Other		1 (2%)	1 (3%)	2 (2%)
Ethnicity - n(%)	Hispanic Or Latino	9 (24%)	11 (25%)	10 (25%)	30 (25%)
	Not Hispanic Or Latino	27 (73%)	33 (75%)	28 (70%)	88 (73%)
	Not Reported	1 (3%)		2 (5%)	3 (2%)
Weight (kg)	Mean (SD)	96.0 (22.04)	97.5 (18.54)	96.0 (22.55)	96.5 (20.85)
	Median	90.0	95.1	93.5	92.0
	Range	58 - 151	69 - 162	56 - 145	56 - 162
Height (cm)	Mean (SD)	167.3 (11.10)	168.1 (9.33)	164.7 (12.23)	166.7 (10.91)
	Median	167.0	169.1	163.8	166.0
	Range	148 - 190	149 - 192	142 - 190	142 - 192
BMI (kg/m^2)	Mean (SD)	34.0 (5.53)	34.5 (5.38)	35.1 (5.47)	34.5 (5.43)
	Median	32.9	33.8	35.0	33.7
	Range	26 - 48	24 - 47	24 - 46	24 - 48

BMI: body mass index

For Cohort 1 (37 patients dosed 100 mg nidufexor and 19 patients dosed placebo) inclusion criteria were: ALT ≥ 60 IU/L (males) or ≥ 40 IU/L (females) at Screening and, for those patients without a histological diagnosis of NASH, BMI ≥ 27 kg/m^2 (in patients with a self-identified race other than Asian) or ≥23 kg/m^2 (in patients with a self-identified Asian race).

For Cohort 2 (44 patients dosed 50 mg nidufexor and 21 patients dosed placebo) inclusion criteria were: ALT ≥ 43 IU/L (males) or ≥ 28 IU/L (females) at Screening and, for those without a histological diagnosis of NASH, BMI ≥ 27 kg/m^2 (in patients with a self-identified race other than Asian) or ≥23 kg/m^2 (in patients with a self-identified Asian race). In both Cohorts 1 and 2, the maximal weight for inclusion was 200 kg.

Primary Outcome Result(s)

Bayesian analysis of change from baseline to Week 12 in ALT (PD analysis set)

Parameter (unit): Alanine Aminotransferase (U/L)

	Posterior estimate of median change from baseline		Posterior estimate of difference in median changes: Test vs Ref.			
Test vs Ref. (Comparison)	**Test**	**Ref**	**Diff. (LMB763-Placebo)**	**90% CI**	**Pr1***	**Pr2****
LMB763 100 mg (N=24) vs Pooled placebo (N=33)	-21.50	-4.76	-16.74	(-28.57, -4.90)	0.990	0.377
LMB763 50 mg (N=40) vs Pooled placebo (N=33)	-12.19	-4.76	-7.43	(-17.69, 2.84)	0.883	0.032

Baseline is defined as the mean of ALT levels at baseline (V2) and pre-dose (V101) visits
A Bayesian approach was used to analyze the change from baseline to Week 12 in ALT, which is assumed to follow a normal distribution with a known variance for both treatment arms. An informative prior worth 6 patients (effective sample size) for the placebo treatment effect based on LJN452A2202 study and a non-informative prior for the LMB763 treatment effect were incorporated in the analysis.
*: Posterior probability that the placebo-adjusted ALT reduction by LMB763 is greater than 0
**: Posterior probability that the placebo-adjusted ALT reduction by LMB763 is greater than 19 U/L

ANCOVA analysis of ratio to baseline in ALT (PD analysis set)

Parameter (unit): Alanine Aminotransferase (U/L)

		[n] Adjusted geometric mean ratio to baseline		Comparison of adjusted geometric mean ratios: Test vs Ref.		
Test vs Ref. (Comparison)	**Visit**	**Test**	**Ref**	**Ratio (Test/Ref)**	**90% CI**	**p-value**

Parameter (unit): Alanine Aminotransferase (U/L)						
		[n] Adjusted geometric mean ratio to baseline		Comparison of adjusted geometric mean ratios: Test vs Ref.		
Test vs Ref. (Comparison)	Visit	Test	Ref	Ratio (Test/Ref)	90% CI	p-value
LMB763 100 mg (N=37) vs LMB763 50 mg (N=44)	Day 7	[36] 0.73	[44] 0.73	1.00	(0.92, 1.10)	0.9583
	Day 14	[32] 0.85	[44] 0.75	1.13	(1.00, 1.29)	0.1120
	Day 28	[29] 0.75	[43] 0.80	0.94	(0.83, 1.07)	0.4136
	Day 42	[25] 0.76	[42] 0.81	0.94	(0.81, 1.09)	0.4991
	Day 56	[25] 0.75	[41] 0.76	0.99	(0.86, 1.14)	0.8968
	Day 84	[24] 0.67	[40] 0.69	0.97	(0.83, 1.13)	0.7489
	EOS	[22] 0.87	[39] 0.83	1.04	(0.90, 1.21)	0.6503
LMB763 100 mg (N=37) vs Pooled placebo (N=40)	Day 7	[36] 0.73	[40] 0.95	0.77	(0.70, 0.84)	<.0001
	Day 14	[32] 0.85	[40] 0.95	0.90	(0.79, 1.02)	0.1663
	Day 28	[29] 0.75	[36] 1.00	0.75	(0.66, 0.85)	0.0003
	Day 42	[25] 0.76	[31] 0.96	0.79	(0.68, 0.92)	0.0112
	Day 56	[25] 0.75	[31] 0.95	0.79	(0.68, 0.91)	0.0061
	Day 84	[24] 0.67	[33] 0.92	0.72	(0.62, 0.84)	0.0005
	EOS	[22] 0.87	[33] 0.95	0.92	(0.79, 1.06)	0.3351
LMB763 50 mg (N=44) vs Pooled placebo (N=40)	Day 7	[44] 0.73	[40] 0.95	0.77	(0.70, 0.83)	<.0001
	Day 14	[44] 0.75	[40] 0.95	0.80	(0.71, 0.89)	0.0016
	Day 28	[43] 0.80	[36] 1.00	0.80	(0.71, 0.90)	0.0027
	Day 42	[42] 0.81	[31] 0.96	0.84	(0.73, 0.97)	0.0395
	Day 56	[41] 0.76	[31] 0.95	0.80	(0.70, 0.91)	0.0044
	Day 84	[40] 0.69	[33] 0.92	0.74	(0.65, 0.85)	0.0005
	EOS	[39] 0.83	[33] 0.95	0.88	(0.77, 1.00)	0.1034

Baseline is defined as the mean of ALT levels at baseline (V2) and pre-dose (V101) visits
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).

An unstructured variance-covariance structure was used.
Estimates were back transformed to the original scale.
The ratio of LMB763 to placebo was estimated for each visit.
N: Number of subjects in each treatment group, n: Number of subjects at each timepoint.

ANCOVA analysis of change from baseline in ALT – PD analysis set

Parameter (unit): Alanine Aminotransferase (U/L)

		[n] Adjusted mean change from baseline (SE)		Comparison of adjusted means: Test vs Ref.			
Test vs Ref. (Comparison)	**Visit**	**Test**	**Ref**	**Diff. (Test-Ref)**	**SE**	**90% CI**	**p-value**
LMB763 100 mg (N=37) vs LMB763 50 mg (N=44)	Day 7	[36] -15.97 (2.23)	[44] -15.77 (2.02)	-0.20	3.08	(-5.30, 4.91)	0.9493
	Day 14	[32] -4.64 (3.45)	[44] -13.90 (2.97)	9.26	4.66	(1.53, 16.98)	0.0492
	Day 28	[29] -14.74 (3.78)	[43] -9.31 (3.23)	-5.43	5.07	(-13.84, 2.98)	0.2866
	Day 42	[25] -13.40 (5.10)	[42] -6.64 (4.14)	-6.76	6.68	(-17.85, 4.32)	0.3136
	Day 56	[25] -13.96 (4.55)	[41] -10.37 (3.73)	-3.59	5.99	(-13.54, 6.36)	0.5505
	Day 84	[24] -19.50 (4.34)	[40] -13.00 (3.48)	-6.51	5.68	(-15.95, 2.94)	0.2552
	EOS	[22] -6.94 (4.38)	[39] -3.60 (3.36)	-3.34	5.64	(-12.72, 6.04)	0.5550
LMB763 100 mg (N=37) vs Pooled placebo (N=40)	Day 7	[36] -15.97 (2.23)	[40] -2.18 (2.07)	-13.79	3.03	(-18.82, -8.77)	<.0001
	Day 14	[32] -4.64 (3.45)	[40] -3.12 (3.05)	-1.52	4.58	(-9.11, 6.07)	0.7399
	Day 28	[29] -14.74 (3.78)	[36] 0.35 (3.40)	-15.09	5.06	(-23.48, -6.70)	0.0035
	Day 42	[25] -13.40 (5.10)	[31] 0.09 (4.56)	-13.49	6.79	(-24.77, -2.22)	0.0496
	Day 56	[25] -13.96 (4.55)	[31] 0.25 (4.06)	-14.21	6.06	(-24.28, -4.15)	0.0210
	Day 84	[24] -19.50 (4.34)	[33] -2.20 (3.71)	-17.30	5.68	(-26.74, -7.85)	0.0031
	EOS	[22] -6.94 (4.38)	[33] -1.24 (3.58)	-5.70	5.63	(-15.07, 3.67)	0.3144
LMB763 50 mg (N=44) vs Pooled placebo (N=40)	Day 7	[44] -15.77 (2.02)	[40] -2.18 (2.07)	-13.60	2.90	(-18.41, -8.78)	<.0001
	Day 14	[44] -13.90 (2.97)	[40] -3.12 (3.05)	-10.78	4.27	(-17.87, -3.69)	0.0131
	Day 28	[43] -9.31 (3.23)	[36] 0.35 (3.40)	-9.66	4.72	(-17.49, -1.83)	0.0430
	Day 42	[42] -6.64 (4.14)	[31] 0.09 (4.56)	-6.73	6.20	(-17.03, 3.57)	0.2806
	Day 56	[41] -10.37 (3.73)	[31] 0.25 (4.06)	-10.62	5.56	(-19.85, -1.39)	0.0589

Parameter (unit): Alanine Aminotransferase (U/L)							
		[n] Adjusted mean change from baseline (SE)		Comparison of adjusted means: Test vs Ref.			
Test vs Ref. (Comparison)	Visit	Test	Ref	Diff. (Test-Ref)	SE	90% CI	p-value
	Day 84	[40] -13.00 (3.48)	[33] -2.20 (3.71)	-10.79	5.12	(-19.32, -2.27)	0.0383
	EOS	[39] -3.60 (3.36)	[33] -1.24 (3.58)	-2.36	4.93	(-10.57, 5.85)	0.6338

Baseline is defined as the mean of ALT levels at baseline (V2) and pre-dose (V101) visits
Change from baseline was analyzed using a repeated measures model which included effects for treatment, visit, treatment by visit interaction, stratification factor (BMI group), baseline and 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).
An unstructured variance-covariance structure was used.
The difference of LMB763 vs placebo was estimated for each visit.
N: Number of subjects in each treatment group, n: Number of subjects at each timepoint.

Secondary Outcome Result(s)

ANCOVA analysis of change from baseline in % liver fat as measured by MRI – PD analysis set

Parameter (unit): Hepatic Fat Fraction (%)							
		[n] Adjusted mean change from baseline (SE)		Comparison of adjusted means: Test vs Ref.			
Test vs Ref. (Comparison)	Visit	Test	Ref	Diff. (Test-Ref)	SE	90% CI	p-value
LMB763 100 mg (N=22) vs LMB763 50 mg (N=41)	Day 84	[22] -6.874 (0.943)	[41] -5.645 (0.695)	-1.229	1.172	(-3.176, 0.718)	0.2970
LMB763 100 mg (N=22) vs Pooled placebo (N=32)	Day 84	[22] -6.874 (0.943)	[32] -0.436 (0.782)	-6.438	1.225	(-8.474, -4.403)	<.0001
LMB763 50 mg (N=41) vs Pooled placebo (N=32)	Day 84	[41] -5.645 (0.695)	[32] -0.436 (0.782)	-5.209	1.047	(-6.950, -3.468)	<.0001

Baseline is defined as the last available measurement prior to the first dose.
Change from baseline was analyzed using an ANCOVA model which included effects for treatment, baseline and stratification factor (BMI group). BMI was separated into two groups, low BMI (Asian<30 and Non-Asian<35) and high BMI (Asian >=30 and Non-Asian>=35).
N: Number of subjects in each treatment group, n: Number of subjects at each timepoint.

ANCOVA analysis of ratio to baseline in % liver fat as measured by MRI – PD analysis set

Parameter (unit): Hepatic Fat Fraction (%)

		[n] Adjusted geometric mean ratio to baseline		Comparison of adjusted geometric mean ratios: Test vs Ref.		
Test vs Ref. (Comparison)	**Visit**	**Test**	**Ref**	**Ratio (Test/Ref)**	**90% CI**	**p-value**
LMB763 100 mg (N=22) vs LMB763 50 mg (N=41)	Day 84	[22] 0.65	[41] 0.68	0.95	(0.83, 1.09)	0.5354
LMB763 100 mg (N=22) vs Pooled placebo (N=32)	Day 84	[22] 0.65	[32] 0.96	0.68	(0.59, 0.78)	<.0001
LMB763 50 mg (N=41) vs Pooled placebo (N=32)	Day 84	[41] 0.68	[32] 0.96	0.71	(0.63, 0.80)	<.0001

Baseline is defined as the last available measurement prior to the first dose.
Log transformed ratio to baseline was analyzed using an ANCOVA model which included effects for treatment, log-transformed baseline and stratification factor (BMI group). BMI was separated into two groups, low BMI (Asian<30 and Non-Asian<35) and high BMI (Asian =30 and Non-Asian=35).
Estimates were back transformed to the original scale.
The ratio of LMB763 to placebo was estimated for each visit.
N: Number of subjects in each treatment group, n: Number of subjects at each timepoint.

Bayesian analysis of change from baseline to Week 12 in % liver fat as measured by MRI – PD analysis set

Parameter (unit): Hepatic Fat Fraction (%)

	Posterior estimate of median change from baseline		Posterior estimate of difference in median changes: Test vs Ref.			
Test vs Ref. (Comparison)	**Test**	**Ref**	**Diff. (LMB763-Placebo)**	**90% CI**	**Pr1***	**Pr2****
LMB763 100 mg (N=22) vs Pooled placebo (N=32)	-6.92	-0.54	-6.39	(-8.76, -4.01)	1.000	0.997
LMB763 50 mg (N=41) vs Pooled placebo (N=32)	-5.58	-0.54	-5.04	(-7.04, -3.04)	1.000	0.983

Baseline is defined as the last available measurement prior to the first dose.
A Bayesian approach was used to analyze the change from baseline to Week 12 in % liver fat as measured by MRI, which is assumed to follow a normal distribution with a known variance for both treatment arms. An informative prior worth 6 patients (effective sample size) for the placebo treatment effect based on LJN452A2202 study and a non-informative prior for the LMB763 treatment effect were incorporated in the analysis.
*: Posterior probability that the placebo-adjusted % liver fat reduction by LMB763 is greater than 0
**: Posterior probability that the placebo-adjusted % liver fat reduction by LMB763 is greater than 2.46%

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Bayesian analysis of percentage change from baseline to Week 12 in % liver fat as measured by MRI – PD analysis set

Parameter (unit): Hepatic Fat Fraction (%)

	Posterior estimate of median percentage change from baseline		Posterior estimate of difference in median percentage changes: Test vs Ref.			
Test vs Ref. (Comparison)	**Test**	**Ref**	**Diff. (LMB763-Placebo)**	**90% CI**	**Pr1***	**Pr2****
LMB763 100 mg (N=22) vs Pooled placebo (N=32)	-32.62	-1.29	-31.34	(-43.41, -19.26)	1.000	0.987
LMB763 50 mg (N=41) vs Pooled placebo (N=32)	-27.28	-1.29	-26.00	(-36.15, -15.85)	1.000	0.963

Baseline is defined as the last available measurement prior to the first dose.
A Bayesian approach was used to analyze the percentage change from baseline to Week 12 in % liver fat as measured by MRI, which is assumed to follow a normal distribution with a known variance for both treatment arms. An informative prior worth 6 patients (effective sample size) for the placebo treatment effect based on LJN452A2202 study and a non-informative prior for the LMB763 treatment effect were incorporated in the analysis.
*: Posterior probability that the placebo-adjusted % liver fat percentage decrease by LMB763 is greater than 0
**: Posterior probability that the placebo-adjusted % liver fat percentage decrease by LMB763 is greater than 15%

ANCOVA analysis of change from baseline in weight – PD analysis set

Parameter (unit): Weight (kg)

		[n] Adjusted mean change from baseline (SE)		Comparison of adjusted means: Test vs Ref.			
Test vs Ref. (Comparison)	**Visit**	**Test**	**Ref**	**Diff. (Test-Ref)**	**SE**	**90% CI**	**p-value**
LMB763 100 mg (N=30) vs LMB763 50 mg (N=43)	Day 28	[30] -0.769 (0.299)	[43] -0.690 (0.251)	-0.079	0.389	(-0.724, 0.567)	0.8402
	Day 42	[27] -1.192 (0.365)	[43] -1.048 (0.301)	-0.144	0.472	(-0.927, 0.639)	0.7607
	Day 56	[26] -1.612 (0.378)	[42] -1.384 (0.309)	-0.228	0.487	(-1.037, 0.581)	0.6406
	Day 84	[24] -2.096 (0.534)	[40] -1.938 (0.430)	-0.158	0.685	(-1.294, 0.979)	0.8185
	EOS	[22] -1.948 (0.602)	[39] -1.734 (0.474)	-0.214	0.766	(-1.485, 1.057)	0.7804
LMB763 100 mg (N=30) vs Pooled placebo (N=37)	Day 28	[30] -0.769 (0.299)	[37] -0.171 (0.269)	-0.598	0.402	(-1.265, 0.070)	0.1403
	Day 42	[27] -1.192 (0.365)	[34] -0.262 (0.327)	-0.930	0.490	(-1.743, -0.117)	0.0603
	Day 56	[26] -1.612 (0.378)	[35] -0.268 (0.334)	-1.344	0.505	(-2.182, -0.506)	0.0090
	Day 84	[24] -2.096 (0.534)	[34] -0.308 (0.467)	-1.787	0.710	(-2.965, -0.609)	0.0134
	EOS	[22] -1.948 (0.602)	[33] 0.175 (0.515)	-2.123	0.793	(-3.439, -0.807)	0.0087
LMB763 50 mg (N=43) vs	Day 28	[43] -0.690 (0.251)	[37] -0.171 (0.269)	-0.519	0.368	(-1.130, 0.091)	0.1609

Parameter (unit): Weight (kg)

		[n] Adjusted mean change from baseline (SE)		Comparison of adjusted means: Test vs Ref.			
Test vs Ref. (Comparison)	**Visit**	**Test**	**Ref**	**Diff. (Test-Ref)**	**SE**	**90% CI**	**p-value**
Pooled placebo (N=37)	Day 42	[43] -1.048 (0.301)	[34] -0.262 (0.327)	-0.786	0.444	(-1.524, -0.049)	0.0797
	Day 56	[42] -1.384 (0.309)	[35] -0.268 (0.334)	-1.116	0.455	(-1.872, -0.360)	0.0159
	Day 84	[40] -1.938 (0.430)	[34] -0.308 (0.467)	-1.630	0.635	(-2.684, -0.575)	0.0118
	EOS	[39] -1.734 (0.474)	[33] 0.175 (0.515)	-1.909	0.700	(-3.072, -0.746)	0.0076

Baseline is defined as the last available measurement prior to the first dose.
Change from baseline was analyzed using a repeated measures model which included effects for treatment, visit, treatment by visit interaction, stratification factor (BMI group), baseline and 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).
An unstructured variance-covariance structure was used.
The difference of LMB763 vs placebo was estimated for each visit.
N: Number of subjects in each treatment group, n: Number of subjects at each timepoint.

ANCOVA analysis of change from baseline in BMI – PD analysis set

Parameter (unit): Body Mass Index (kg/m^2)

		[n] Adjusted mean change from baseline (SE)		Comparison of adjusted means: Test vs Ref.			
Test vs Ref. (Comparison)	**Visit**	**Test**	**Ref**	**Diff. (Test-Ref)**	**SE**	**90% CI**	**p-value**
LMB763 100 mg (N=30) vs LMB763 50 mg (N=43)	Day 28	[30] -0.283 (0.105)	[43] -0.251 (0.088)	-0.033	0.137	(-0.260, 0.195)	0.8127
	Day 42	[27] -0.412 (0.128)	[43] -0.389 (0.106)	-0.023	0.166	(-0.298, 0.252)	0.8901
	Day 56	[26] -0.581 (0.137)	[42] -0.494 (0.112)	-0.088	0.177	(-0.381, 0.205)	0.6209
	Day 84	[24] -0.747 (0.186)	[40] -0.699 (0.150)	-0.048	0.238	(-0.444, 0.347)	0.8398
	EOS	[22] -0.690 (0.209)	[39] -0.617 (0.165)	-0.073	0.266	(-0.515, 0.369)	0.7839
LMB763 100 mg (N=30) vs Pooled placebo (N=37)	Day 28	[30] -0.283 (0.105)	[37] -0.042 (0.095)	-0.241	0.141	(-0.476, -0.006)	0.0911
	Day 42	[27] -0.412 (0.128)	[34] -0.074 (0.115)	-0.338	0.172	(-0.623, -0.053)	0.0520
	Day 56	[26] -0.581 (0.137)	[35] -0.091 (0.121)	-0.490	0.183	(-0.793, -0.187)	0.0085
	Day 84	[24] -0.747 (0.186)	[34] -0.090 (0.163)	-0.657	0.247	(-1.067, -0.247)	0.0091
	EOS	[22] -0.690 (0.209)	[33] 0.069 (0.180)	-0.759	0.275	(-1.216, -0.302)	0.0070

Parameter (unit): Body Mass Index (kg/m^2)

Test vs Ref. (Comparison)	Visit	[n] Adjusted mean change from baseline (SE)		Comparison of adjusted means: Test vs Ref.			
		Test	Ref	Diff. (Test-Ref)	SE	90% CI	p-value
LMB763 50 mg (N=43) vs Pooled placebo (N=37)	Day 28	[43] -0.251 (0.088)	[37] -0.042 (0.095)	-0.208	0.129	(-0.423, 0.006)	0.1092
	Day 42	[43] -0.389 (0.106)	[34] -0.074 (0.115)	-0.315	0.156	(-0.574, -0.056)	0.0457
	Day 56	[42] -0.494 (0.112)	[35] -0.091 (0.121)	-0.402	0.165	(-0.676, -0.129)	0.0162
	Day 84	[40] -0.699 (0.150)	[34] -0.090 (0.163)	-0.608	0.221	(-0.975, -0.242)	0.0070
	EOS	[39] -0.617 (0.165)	[33] 0.069 (0.180)	-0.686	0.244	(-1.091, -0.281)	0.0060

Change from baseline was analyzed using a repeated measures model which included effects for treatment, visit, treatment by visit interaction, stratification factor (BMI group), baseline and 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).
An unstructured variance-covariance structure was used.
The difference of LMB763 vs placebo was estimated for each visit.
N: Number of subjects in each treatment group, n: Number of subjects at each timepoint.

ANCOVA analysis of change from baseline in anthropometric assessments (Waist To Hip Ratio) – PD analysis set

Parameter (unit): Waist To Hip Ratio

Test vs Ref. (Comparison)	Visit	[n] Adjusted mean change from baseline (SE)		Comparison of adjusted means: Test vs Ref.			
		Test	Ref	Diff. (Test-Ref)	SE	90% CI	p-value
LMB763 100 mg (N=30) vs LMB763 50 mg (N=43)	Day 28	[30] 0.001 (0.007)	[43] 0.001 (0.006)	-0.000	0.009	(-0.015, 0.014)	0.9927
	Day 42	[27] 0.012 (0.010)	[40] -0.002 (0.008)	0.014	0.013	(-0.007, 0.035)	0.2794
	Day 56	[25] -0.003 (0.006)	[42] -0.004 (0.005)	0.001	0.007	(-0.012, 0.013)	0.9032
	Day 84	[24] 0.001 (0.009)	[40] -0.008 (0.007)	0.009	0.011	(-0.009, 0.027)	0.4163
	EOS	[22] -0.004 (0.009)	[39] -0.000 (0.007)	-0.004	0.011	(-0.022, 0.014)	0.7001
LMB763 100 mg (N=30) vs Pooled placebo (N=37)	Day 28	[30] 0.001 (0.007)	[36] -0.005 (0.006)	0.006	0.009	(-0.009, 0.021)	0.5367
	Day 42	[27] 0.012 (0.010)	[34] 0.004 (0.009)	0.008	0.013	(-0.014, 0.030)	0.5496
	Day 56	[25] -0.003 (0.006)	[34] -0.006 (0.005)	0.003	0.008	(-0.010, 0.016)	0.6844
	Day 84	[24] 0.001 (0.009)	[34] 0.008 (0.007)	-0.007	0.011	(-0.025, 0.012)	0.5695
	EOS	[22] -0.004 (0.009)	[33] -0.001 (0.007)	-0.003	0.011	(-0.021, 0.016)	0.8015

Parameter (unit): Waist To Hip Ratio

		[n] Adjusted mean change from baseline (SE)		Comparison of adjusted means: Test vs Ref.			
Test vs Ref. (Comparison)	**Visit**	**Test**	**Ref**	**Diff. (Test-Ref)**	**SE**	**90% CI**	**p-value**
LMB763 50 mg (N=43) vs Pooled placebo (N=37)	Day 28	[43] 0.001 (0.006)	[36] -0.005 (0.006)	0.006	0.008	(-0.008, 0.020)	0.4923
	Day 42	[40] -0.002 (0.008)	[34] 0.004 (0.009)	-0.006	0.012	(-0.025, 0.014)	0.6200
	Day 56	[42] -0.004 (0.005)	[34] -0.006 (0.005)	0.002	0.007	(-0.009, 0.014)	0.7423
	Day 84	[40] -0.008 (0.007)	[34] 0.008 (0.007)	-0.016	0.010	(-0.032, 0.001)	0.1272
	EOS	[39] -0.000 (0.007)	[33] -0.001 (0.007)	0.001	0.010	(-0.015, 0.017)	0.8883

Baseline is defined as the last available measurement prior to the first dose.
Change from baseline was analyzed using a repeated measures model which included effects for treatment, visit, treatment by visit interaction, stratification factor (BMI group), baseline and 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).
An unstructured variance-covariance structure was used.
The difference of LMB763 vs placebo was estimated for each visit.
N: Number of subjects in each treatment group, n: Number of subjects at each timepoint.

ANCOVA analysis of ratio to baseline in liver stiffness (kPa) – PD analysis set

Parameter (unit): Liver Stiffness (kPa)

		Adjusted geometric mean ratio to baseline		Comparison of adjusted geometric mean ratios: Test vs Ref.		
Test vs Ref. (Comparison)	**Visit**	**Test**	**Ref**	**Ratio (LMB763/Placebo)**	**90% CI**	**p-value**
LMB763 100 mg (N=7) vs LMB763 50 mg (N=15)	Day 84	[7] 1.03	[15] 1.02	1.01	(0.84, 1.21)	0.9514
LMB763 100 mg (N=7) vs Pooled placebo (N=16)	Day 84	[7] 1.03	[16] 1.10	0.93	(0.78, 1.12)	0.5168
LMB763 50 mg (N=15) vs Pooled placebo (N=16)	Day 84	[15] 1.02	[16] 1.10	0.93	(0.80, 1.07)	0.3740

Baseline is defined as the last available measurement prior to the first dose.
Log transformed ratio to baseline was analyzed using an ANCOVA model which included effects for treatment, log-transformed baseline and stratification factor (BMI group).
BMI was separated into two groups, low BMI (Asian<30 and Non-Asian<35) and high BMI (Asian =30 and Non-Asian=35).
Estimates were back transformed to the original scale.
The ratio of LMB763 to placebo was estimated for each visit.
N: Number of subjects in each treatment group, n: Number of subjects at each timepoint.

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ANCOVA analysis of ratio to baseline in liver stiffness (kPa) - sensitivity analysis (PD analysis set)

Parameter (unit): Liver Stiffness (kPa)

		Adjusted geometric mean ratio to baseline		Comparison of adjusted geometric mean ratios: Test vs Ref.		
Test vs Ref. (Comparison)	**Visit**	**Test**	**Ref**	**Ratio (LMB763/Placebo)**	**90% CI**	**p-value**
LMB763 100 mg (N=6) vs LMB763 50 mg (N=15)	Day 84	[6] 0.94	[15] 1.03	0.92	(0.77, 1.09)	0.4147
LMB763 100 mg (N=6) vs Pooled placebo (N=15)	Day 84	[6] 0.94	[15] 1.02	0.92	(0.77, 1.09)	0.4082
LMB763 50 mg (N=15) vs Pooled placebo (N=15)	Day 84	[15] 1.03	[15] 1.02	1.00	(0.88, 1.15)	0.9812

Baseline is defined as the last available measurement prior to the first dose.
Log transformed ratio to baseline was analyzed using an ANCOVA model which included effects for treatment, log-transformed baseline and stratification factor (BMI group). BMI was separated into two groups, low BMI (Asian<30 and Non-Asian<35) and high BMI (Asian =30 and Non-Asian=35).
Estimates were back transformed to the original scale.
The ratio of LMB763 to placebo was estimated for each visit.
N: Number of subjects in each treatment group, n: Number of subjects at each timepoint.
Three patients were excluded from the liver stiffness parameter, whereas one patient was excluded from the CAP parameter due to poor data quality.

ANCOVA analysis of ratio to baseline in enhanced liver fibrosis panel (ELF) – PD analysis set

Parameter (unit): ELF Score

		[n] Adjusted geometric mean ratio to baseline		Comparison of adjusted geometric mean ratios: Test vs Ref.		
Test vs Ref. (Comparison)	**Visit**	**Test**	**Ref**	**Ratio (Test/Ref)**	**90% CI**	**p-value**
LMB763 100 mg (N=27) vs LMB763 50 mg (N=42)	Day 42	[26] 1.01	[42] 1.01	1.00	(0.97, 1.02)	0.9453
	Day 84	[24] 1.01	[37] 1.02	0.99	(0.96, 1.01)	0.4344
LMB763 100 mg (N=27) vs Pooled placebo (N=35)	Day 42	[26] 1.01	[33] 1.02	0.99	(0.97, 1.02)	0.6390
	Day 84	[24] 1.01	[33] 1.02	0.99	(0.97, 1.02)	0.6329
LMB763 50 mg (N=42) vs Pooled placebo (N=35)	Day 42	[42] 1.01	[33] 1.02	0.99	(0.97, 1.02)	0.6640
	Day 84	[37] 1.02	[33] 1.02	1.00	(0.98, 1.03)	0.7517

Baseline is defined as the last available measurement prior to the first dose.
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).

An unstructured variance-covariance structure was used.
Estimates were back transformed to the original scale. The ratio of LMB763 to placebo was estimated for each visit.
When calculating changes from baseline, values below the LLOQ were replaced by 0.5 x LLOQ and values above the ULOQ were replaced by 1.0 x ULOQ.
N: Number of subjects in each treatment group, n: Number of subjects at each timepoint.

ANCOVA analysis of ratio to baseline in Fibroscan parameters - sensitivity analysis (PD analysis set)

Parameter (unit): Controlled Attenuation Parameter (dB/m)

		Adjusted geometric mean ratio to baseline		Comparison of adjusted geometric mean ratios: Test vs Ref.		
Test vs Ref. (Comparison)	**Visit**	**Test**	**Ref**	**Ratio (LMB763/Placebo)**	**90% CI**	**p-value**
LMB763 100 mg (N=5) vs LMB763 50 mg (N=14)	Day 84	[5] 0.95	[14] 0.89	1.06	(0.96, 1.18)	0.3103
LMB763 100 mg (N=5) vs Pooled placebo (N=12)	Day 84	[5] 0.95	[12] 0.94	1.02	(0.91, 1.13)	0.8067
LMB763 50 mg (N=14) vs Pooled placebo (N=12)	Day 84	[14] 0.89	[12] 0.94	0.95	(0.88, 1.03)	0.3088

Baseline is defined as the last available measurement prior to the first dose.
Log transformed ratio to baseline was analyzed using an ANCOVA model which included effects for treatment, log-transformed baseline and stratification factor (BMI group).
BMI was separated into two groups, low BMI (Asian<30 and Non-Asian<35) and high BMI (Asian =30 and Non-Asian=35).
Estimates were back transformed to the original scale.
The ratio of LMB763 to placebo was estimated for each visit.
N: Number of subjects in each treatment group, n: Number of subjects at each timepoint.
Three patients were excluded from the liver stiffness parameter, whereas one patient was excluded from the CAP parameter due to poor data quality.

ANCOVA analysis of change from baseline in Visual Analog Scale (VAS) for itching of the skin – PD analysis set

Parameter (unit): Visual Analogue Scale- Itch (mm)

		[n] Adjusted mean change from baseline (SE)		Comparison of adjusted means: Test vs Ref.			
Test vs Ref. (Comparison)	**Visit**	**Test**	**Ref**	**Diff. (Test-Ref)**	**SE**	**90% CI**	**p-value**
LMB763 100 mg (N=23) vs LMB763 50 mg (N=39)	Day 84	[23] 10.07 (4.34)	[39] 3.07 (3.38)	7.01	5.52	(-2.161, 16.178)	0.2073

Parameter (unit): Visual Analogue Scale- Itch (mm)							
		[n] Adjusted mean change from baseline (SE)		Comparison of adjusted means: Test vs Ref.			
Test vs Ref. (Comparison)	Visit	Test	Ref	Diff. (Test-Ref)	SE	90% CI	p-value
LMB763 100 mg (N=23) vs Pooled placebo (N=34)	Day 84	[23] 10.07 (4.34)	[34] 2.85 (3.58)	7.23	5.62	(-2.106, 16.563)	0.2014
LMB763 50 mg (N=39) vs Pooled placebo (N=34)	Day 84	[39] 3.07 (3.38)	[34] 2.85 (3.58)	0.22	4.93	(-7.974, 8.414)	0.9645

Baseline is defined as the last available measurement prior to the first dose.
Change from baseline was analyzed using an ANCOVA model which included effects for treatment, baseline and stratification factor (BMI group). BMI was separated into two groups, low BMI (Asian<30 and Non-Asian<35) and high BMI (Asian >=30 and Non-Asian>=35).
N: Number of subjects in each treatment group, n: Number of subjects at each timepoint.

Safety Results

Incidence of AEs by primary system organ class- n (percent) of patients (Part 1)

	LMB763			
	100 mg N=37 n (%)	50 mg N=44 n (%)	Pooled placebo N=40 n (%)	Total N=121 n (%)
Patients with at least one AE	35 (94.6)	37 (84.1)	33 (82.5)	105 (86.8)
System organ class				
Skin and subcutaneous tissue disorders	24 (64.9)	14 (31.8)	11 (27.5)	49 (40.5)
Investigations	20 (54.1)	13 (29.5)	15 (37.5)	48 (39.7)
Gastrointestinal disorders	16 (43.2)	12 (27.3)	13 (32.5)	41 (33.9)
Infections and infestations	12 (32.4)	18 (40.9)	11 (27.5)	41 (33.9)
Nervous system disorders	8 (21.6)	13 (29.5)	10 (25.0)	31 (25.6)
Musculoskeletal and connective tissue disorders	1 (2.7)	6 (13.6)	10 (25.0)	17 (14.0)

	LMB763			
	100 mg N=37 n (%)	50 mg N=44 n (%)	Pooled placebo N=40 n (%)	Total N=121 n (%)
Respiratory, thoracic and mediastinal disorders	9 (24.3)	3 (6.8)	5 (12.5)	17 (14.0)
General disorders and administration site conditions	7 (18.9)	2 (4.5)	5 (12.5)	14 (11.6)
Metabolism and nutrition disorders	5 (13.5)	8 (18.2)	0	13 (10.7)
Injury, poisoning and procedural complications	4 (10.8)	4 (9.1)	4 (10.0)	12 (9.9)
Renal and urinary disorders	1 (2.7)	4 (9.1)	5 (12.5)	10 (8.3)
Psychiatric disorders	2 (5.4)	3 (6.8)	3 (7.5)	8 (6.6)
Vascular disorders	2 (5.4)	0	2 (5.0)	4 (3.3)
Ear and labyrinth disorders	1 (2.7)	1 (2.3)	1 (2.5)	3 (2.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (2.7)	1 (2.3)	1 (2.5)	3 (2.5)
Hepatobiliary disorders	1 (2.7)	1 (2.3)	0	2 (1.7)
Immune system disorders	2 (5.4)	0	0	2 (1.7)
Reproductive system and breast disorders	1 (2.7)	0	1 (2.5)	2 (1.7)
Blood and lymphatic system disorders	1 (2.7)	0	0	1 (0.8)
Cardiac disorders	0	0	1 (2.5)	1 (0.8)
Eye disorders	0	1 (2.3)	0	1 (0.8)

Arranged in descending order of frequency (in total group) and alphabetically by system organ class

Only adverse events occurring at or after first drug intake are included.

Incidence of AEs (=>5%) by preferred term - n (percent) of patients (Safety analysis set)

	LMB763			
	100 mg N=37 n (%)	50 mg N=44 n (%)	Pooled placebo N=40 n (%)	Total N=121 n (%)

	LMB763			
	100 mg N=37 n (%)	50 mg N=44 n (%)	Pooled placebo N=40 n (%)	Total N=121 n (%)
Patients with at least one AE	35 (94.6)	37 (84.1)	33 (82.5)	105 (86.8)
Preferred term				
Pruritus	20 (54.1)	13 (29.5)	6 (15.0)	39 (32.2)
Headache	3 (8.1)	7 (15.9)	8 (20.0)	18 (14.9)
Urine protein/creatinine ratio increased	7 (18.9)	8 (18.2)	3 (7.5)	18 (14.9)
Nausea	7 (18.9)	5 (11.4)	2 (5.0)	14 (11.6)
Diarrhoea	4 (10.8)	4 (9.1)	4 (10.0)	12 (9.9)
Urine albumin/creatinine ratio increased	2 (5.4)	4 (9.1)	5 (12.5)	11 (9.1)
Neutrophil count decreased	4 (10.8)	1 (2.3)	4 (10.0)	9 (7.4)
Abdominal pain upper	3 (8.1)	2 (4.5)	3 (7.5)	8 (6.6)
Fatigue	2 (5.4)	2 (4.5)	4 (10.0)	8 (6.6)
Hyperglycaemia	4 (10.8)	4 (9.1)	0	8 (6.6)
Upper respiratory tract infection	2 (5.4)	4 (9.1)	2 (5.0)	8 (6.6)
Alanine aminotransferase increased	1 (2.7)	2 (4.5)	4 (10.0)	7 (5.8)
Cough	3 (8.1)	2 (4.5)	2 (5.0)	7 (5.8)
Aspartate aminotransferase increased	4 (10.8)	1 (2.3)	1 (2.5)	6 (5.0)
Influenza	1 (2.7)	1 (2.3)	4 (10.0)	6 (5.0)
Nasopharyngitis	1 (2.7)	2 (4.5)	3 (7.5)	6 (5.0)
Back pain	1 (2.7)	3 (6.8)	1 (2.5)	5 (4.1)
Dyspepsia	2 (5.4)	0	3 (7.5)	5 (4.1)
Pain in extremity	0	2 (4.5)	3 (7.5)	5 (4.1)
Renal disorder	0	4 (9.1)	1 (2.5)	5 (4.1)
Urinary tract infection	0	2 (4.5)	3 (7.5)	5 (4.1)
Viral infection	0	4 (9.1)	1 (2.5)	5 (4.1)
Abdominal distension	0	2 (4.5)	2 (5.0)	4 (3.3)
Abdominal pain	1 (2.7)	0	3 (7.5)	4 (3.3)

	LMB763			
	100 mg N=37 n (%)	50 mg N=44 n (%)	Pooled placebo N=40 n (%)	Total N=121 n (%)
Anxiety	0	1 (2.3)	3 (7.5)	4 (3.3)
Blood alkaline phosphatase increased	3 (8.1)	1 (2.3)	0	4 (3.3)
Blood creatinine increased	3 (8.1)	1 (2.3)	0	4 (3.3)
Blood glucose increased	1 (2.7)	1 (2.3)	2 (5.0)	4 (3.3)
Constipation	4 (10.8)	0	0	4 (3.3)
Dizziness	0	3 (6.8)	1 (2.5)	4 (3.3)
Influenza like illness	4 (10.8)	0	0	4 (3.3)
Insomnia	2 (5.4)	2 (4.5)	0	4 (3.3)
Lymphocyte count increased	2 (5.4)	0	2 (5.0)	4 (3.3)
Paraesthesia	1 (2.7)	3 (6.8)	0	4 (3.3)
Rash pruritic	4 (10.8)	0	0	4 (3.3)
Sinusitis	2 (5.4)	2 (4.5)	0	4 (3.3)
Vomiting	1 (2.7)	3 (6.8)	0	4 (3.3)
Blood creatine phosphokinase increased	0	0	3 (7.5)	3 (2.5)
Contusion	1 (2.7)	0	2 (5.0)	3 (2.5)
Gamma-glutamyltransferase increased	1 (2.7)	0	2 (5.0)	3 (2.5)
Hypertriglyceridaemia	0	3 (6.8)	0	3 (2.5)
Lymphocyte count decreased	3 (8.1)	0	0	3 (2.5)
Musculoskeletal pain	0	0	3 (7.5)	3 (2.5)
Decreased appetite	2 (5.4)	0	0	2 (1.7)
Eosinophil count increased	0	0	2 (5.0)	2 (1.7)
Faeces pale	2 (5.4)	0	0	2 (1.7)
Hypoglycaemia	2 (5.4)	0	0	2 (1.7)
Oral herpes	2 (5.4)	0	0	2 (1.7)
Pruritus generalised	2 (5.4)	0	0	2 (1.7)
Rash erythematous	2 (5.4)	0	0	2 (1.7)

Arranged in descending order of frequency (in total group) and alphabetically by preferred term

Only adverse events occurring at or after first drug intake are included.

Serious Adverse Events and Deaths

No patients died during the study.

Other Relevant Findings

Summary statistics of plasma PK parameter values on Days 1 and 42 - Pharmacokinetic analysis set

Compound: LMB763 , Matrix: PLASMA , Analyte: LMB763

PK parameter (Unit)	Profile day	LMB763 100 mg N=37	LMB763 50 mg N=43
AUCall (h*ng/mL)	1	11200 ± 4740 (42.3%) [37]	4400 ± 2340 (53.1%) [43]
	42	8590 ± 4090 (47.7%) [23]	5180 ± 2870 (55.5%) [42]
AUClast (h*ng/mL)	1	11200 ± 4740 (42.3%) [37]	4360 ± 2350 (53.9%) [42]
	42	8570 ± 4120 (48.0%) [23]	5180 ± 2870 (55.5%) [42]
Accumulation Ratio	42	0.903 ± 0.472 (52.3%) [24]	1.31 ± 0.641 (48.9%) [42]
Clast (ng/mL)	1	1310 ± 589 (44.8%) [37]	666 ± 430 (64.6%) [42]
	42	1010 ± 398 (39.3%) [23]	687 ± 416 (60.6%) [42]
Cmax (ng/mL)	1	3080 ± 1360 (44.2%) [37]	1290 ± 620 (48.0%) [43]
	42	2230 ± 1190 (53.3%) [23]	1290 ± 690 (53.7%) [42]
Tlast (h)	1	6.01 ± 0.124 (2.1%) [37]	5.99 ± 0.0867 (1.4%) [42]
	42	5.90 ± 0.411 (7.0%) [24]	5.99 ± 0.0748 (1.2%) [42]
Tmax (h)	1	2.00 (1.00 - 6.00) [37]	2.00 (1.00 - 6.08) [43]
	42	2.03 (1.00 - 6.03) [24]	2.02 (1.00 - 6.00) [42]

Statistics are Mean ± SD (CV%) [N]

CV% = Coefficient of variation (%) = (sd/mean)*100

For Tmax, Statistics are Median (Min-Max) [N]

Summary statistics of plasma PK parameter values of LQT724 on Days 1 and 42 - PK analysis set

Compound: LMB763 , Matrix: PLASMA , Analyte: LQT724

PK parameter (Unit)	Profile day	LMB763 100 mg N=37	LMB763 50 mg N=43
AUCall (h*ng/mL)	1	8530 ± 4060 (47.6%) [37]	3270 ± 1580 (48.3%) [43]
	42	8090 ± 5400 (66.8%) [23]	4280 ± 2600 (60.8%) [42]
AUClast (h*ng/mL)	1	8530 ± 4060 (47.6%) [37]	3310 ± 1570 (47.3%) [42]
	42	8040 ± 5440 (67.6%) [23]	4280 ± 2600 (60.8%) [42]
Accumulation Ratio	42	0.997 ± 0.433 (43.5%) [24]	1.34 ± 0.585 (43.7%) [42]
Clast (ng/mL)	1	1310 ± 577 (44.2%) [37]	569 ± 234 (41.2%) [42]
	42	1150 ± 506 (43.9%) [23]	647 ± 380 (58.8%) [42]
Cmax (ng/mL)	1	2200 ± 978 (44.4%) [37]	881 ± 413 (46.9%) [43]
	42	1850 ± 1280 (69.4%) [23]	971 ± 614 (63.2%) [42]
Tlast (h)	1	6.01 ± 0.124 (2.1%) [37]	5.96 ± 0.263 (4.4%) [43]
	42	5.90 ± 0.411 (7.0%) [24]	5.99 ± 0.0748 (1.2%) [42]
Tmax (h)	1	2.05 (1.02 - 6.00) [37]	2.03 (1.37 - 6.08) [43]
	42	2.11 (1.08 - 6.03) [24]	2.13 (1.00 - 6.00) [42]

Statistics are Mean ± SD (CV%) [N]

CV% = Coefficient of variation (%) = (sd/mean)*100

For Tmax, Statistics are Median (Min-Max) [N]

Conclusion:

- Nidufexor was safe and generally well tolerated at 50 mg daily dose for a period of 12 weeks in patients with phenotypic NASH.
- The most common AE was itch, which was viewed as a tolerability rather than a safety signal.
- Overall nidufexor at both 50 mg and 100 mg decreased hepatic ALT levels and hepatic fat fraction by MRI.
- An increase in FGF19 (marker of target engagement) in gut was observed in both dose levels for LMB763 together with decreases in circulating bile acids and C4 levels.
- No meaningful change in total cholesterol, LDL cholesterol or triglycerides were observed, although the expected decrease in HDL cholesterol was seen.

- Taken together, these data further define the further development strategy for nidufexor.

Date of Clinical Trial Report

2 March 2020