Clinical trial results:
A Phase 2b Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of MK-3655 in Individuals With Pre-cirrhotic Nonalcoholic Steatohepatitis (NASH)

Summary

EudraCT number	2019-003048-63
Trial protocol	DE FR IT SE GR
Global end of trial date	13 April 2023

Results information

Result version number	v2 (current)
This version publication date	18 May 2024
First version publication date	29 March 2024
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	3655-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04583423
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme LLC
Sponsor organisation address	126 East Lincoln Avenue, P.O. Box 2000, Rahway, NJ, United States, 07065
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme LLC, ClinicalTrialsDisclosure@merck.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 April 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 April 2023
Global end of trial reached?	Yes
Global end of trial date	13 April 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This study will evaluate the effect of each dose of MK-3655 versus placebo on the percentage of individuals with NASH resolution without worsening of fibrosis after 52 weeks. The primary hypothesis of the study is that at least 1 dose of MK-3655 is superior to placebo with respect to the percentage of individuals with NASH resolution without worsening of fibrosis after 52 weeks.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 November 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 2
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Chile: 3
Country: Number of subjects enrolled	China: 8
Country: Number of subjects enrolled	Colombia: 1
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Hong Kong: 4
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Japan: 45
Country: Number of subjects enrolled	Korea, Republic of: 2
Country: Number of subjects enrolled	Mexico: 6
Country: Number of subjects enrolled	New Zealand: 3
Country: Number of subjects enrolled	Puerto Rico: 5
Country: Number of subjects enrolled	Russian Federation: 6
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Taiwan: 4
Country: Number of subjects enrolled	Türkiye: 3

Country: Number of subjects enrolled	United States: 57
Worldwide total number of subjects	183
EEA total number of subjects	27

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)	141
From 65 to 84 years	42
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Males and females with pre-cirrhotic NASH aged 18 to 80 years (in Japan and Taiwan, aged 20 to 80 years were enrolled in the study

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	MK-3655 50 mg

Arm description:

Following a 2-week placebo run-in, participants received MK-3655 50 mg by subcutaneous (SC) injection once every 4 weeks (Q4W) for 52 weeks.

Arm type	Experimental
Investigational medicinal product name	MK-3655
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

50-mg SC injection Q4W for 52 weeks

Arm title	MK-3655 100 mg

Arm description:

Following a 2-week placebo run-in, participants received MK-3655 100 mg by SC injection Q4W for 52 weeks.

Arm type	Experimental
Investigational medicinal product name	MK-3655
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

100-mg SC injection Q4W for 52 weeks

Arm title	MK-3655 300 mg

Arm description:

Following a 2-week placebo run-in, participants received MK-3655 300 mg by SC injection Q4W for 52 weeks.

Arm type	Experimental

Investigational medicinal product name	MK-3655
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:
300-mg SC injection Q4W for 52 weeks

Arm title	Placebo

Arm description:
Following a 2-week placebo run-in, participants received placebo by SC injection Q4W for 52 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo for MK-3655
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:
SC injection Q4W for 52 weeks

Number of subjects in period 1	MK-3655 50 mg	MK-3655 100 mg	MK-3655 300 mg
Started	45	48	46
Received 1st Dose	45	47	46
Completed	10	11	8
Not completed	35	37	38
Consent withdrawn by subject	3	1	2
Study Terminated by Sponsor	32	35	36
Lost to follow-up	-	1	-

Number of subjects in period 1	Placebo
Started	44
Received 1st Dose	44
Completed	8
Not completed	36
Consent withdrawn by subject	1
Study Terminated by Sponsor	33
Lost to follow-up	2

Baseline characteristics

Reporting groups	
Reporting group title	MK-3655 50 mg
Reporting group description:	
Following a 2-week placebo run-in, participants received MK-3655 50 mg by subcutaneous (SC) injection once every 4 weeks (Q4W) for 52 weeks.	
Reporting group title	MK-3655 100 mg
Reporting group description:	
Following a 2-week placebo run-in, participants received MK-3655 100 mg by SC injection Q4W for 52 weeks.	
Reporting group title	MK-3655 300 mg
Reporting group description:	
Following a 2-week placebo run-in, participants received MK-3655 300 mg by SC injection Q4W for 52 weeks.	
Reporting group title	Placebo
Reporting group description:	
Following a 2-week placebo run-in, participants received placebo by SC injection Q4W for 52 weeks.	

Reporting group values	MK-3655 50 mg	MK-3655 100 mg	MK-3655 300 mg
Number of subjects	45	48	46
Age categorical Units: Participants			
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)	33	38	34
From 65-84 years	12	10	12
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	59.6	54.3	56.6
standard deviation	± 8.9	± 12.3	± 11.3
Sex: Female, Male Units: Participants			
Female	25	20	23
Male	20	28	23
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	15	18	16
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	3	2	1
White	26	28	27
More than one race	0	0	1

Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	12	13	17
Not Hispanic or Latino	33	34	28
Unknown or Not Reported	0	1	1
Fibrosis Score			
The NASH Clinical Research Network (CRN) scoring system assesses NASH activity and fibrosis stage based on the following scoring scales: lobular inflammation score (0-3); hepatocyte ballooning score (0-2); steatosis score (0-3); and fibrosis score (0-4). The Nonalcoholic Fatty Liver Disease (NAFLD) Activity Score (NAS) was calculated as the unweighted sum of the scores for inflammation, ballooning, and steatosis and ranged from 0-8 (highest activity).			
Units: Subjects			
Stage 2	21	22	21
Stage 3	24	26	25
Percent Liver Fat Content			
Assessed via Magnetic Resonance Imaging-Estimated Proton Density Fat Fraction (MRI-PDFF), a highly accurate noninvasive measure of the proportion of fat content of a tissue.			
Units: Subjects			
<20%	30	23	30
≥ 20%	15	25	16
Type 2 Diabetes Mellitus (T2DM) Units: Subjects			
Yes for T2DM	22	25	25
No for T2DM	23	23	21
Region Units: Subjects			
Japan	11	12	11
East Asia excluding Japan	6	5	5
Other	28	31	30

Reporting group values	Placebo	Total	
Number of subjects	44	183	
Age categorical Units: Participants			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	36	141	
From 65-84 years	8	42	
85 years and over	0	0	
Age Continuous Units: Years			
arithmetic mean	55.8		
standard deviation	± 10.1	-	
Sex: Female, Male Units: Participants			
Female	19	87	

Male	25	96	

Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	1	
Asian	16	65	
Native Hawaiian or Other Pacific Islander	0	2	
Black or African American	1	7	
White	26	107	
More than one race	0	1	
Unknown or Not Reported	0	0	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	18	60	
Not Hispanic or Latino	25	120	
Unknown or Not Reported	1	3	
Fibrosis Score			
The NASH Clinical Research Network (CRN) scoring system assesses NASH activity and fibrosis stage based on the following scoring scales: lobular inflammation score (0-3); hepatocyte ballooning score (0-2); steatosis score (0-3); and fibrosis score (0-4). The Nonalcoholic Fatty Liver Disease (NAFLD) Activity Score (NAS) was calculated as the unweighted sum of the scores for inflammation, ballooning, and steatosis and ranged from 0-8 (highest activity).			
Units: Subjects			
Stage 2	21	85	
Stage 3	23	98	
Percent Liver Fat Content			
Assessed via Magnetic Resonance Imaging-Estimated Proton Density Fat Fraction (MRI-PDFF), a highly accurate noninvasive measure of the proportion of fat content of a tissue.			
Units: Subjects			
<20%	31	114	
≥ 20%	13	69	
Type 2 Diabetes Mellitus (T2DM) Units: Subjects			
Yes for T2DM	24	96	
No for T2DM	20	87	
Region Units: Subjects			
Japan	11	45	
East Asia excluding Japan	5	21	
Other	28	117	

End points

End points reporting groups

Reporting group title	MK-3655 50 mg
Reporting group description:	
Following a 2-week placebo run-in, participants received MK-3655 50 mg by subcutaneous (SC) injection once every 4 weeks (Q4W) for 52 weeks.	
Reporting group title	MK-3655 100 mg
Reporting group description:	
Following a 2-week placebo run-in, participants received MK-3655 100 mg by SC injection Q4W for 52 weeks.	
Reporting group title	MK-3655 300 mg
Reporting group description:	
Following a 2-week placebo run-in, participants received MK-3655 300 mg by SC injection Q4W for 52 weeks.	
Reporting group title	Placebo
Reporting group description:	
Following a 2-week placebo run-in, participants received placebo by SC injection Q4W for 52 weeks.	

Primary: Percentage of Participants With Nonalcoholic Steatohepatitis (NASH) Resolution Without Worsening of Fibrosis After 52 Weeks

End point title	Percentage of Participants With Nonalcoholic Steatohepatitis (NASH) Resolution Without Worsening of Fibrosis After 52 Weeks
End point description:	
The NASH Clinical Research Network (CRN) scoring system evaluated by Blinded Independent Central Review (BICR) was used to assess treatment response. The NASH CRN scoring scales were: lobular inflammation score (0-3); hepatocyte ballooning score (0-2); steatosis score (0-3); and fibrosis score (0-4). NASH resolution was defined as a score of 0-1 for inflammation, 0 for ballooning, and any grade of steatosis. Analysis population was the Full Analysis Set (FAS), which consisted of all randomized participants who had at least 1 injection of study intervention and had at least 1 assessment.	
End point type	Primary
End point timeframe:	
Week 52	

End point values	MK-3655 50 mg	MK-3655 100 mg	MK-3655 300 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	21	17	17
Units: Percentage of Participants				
number (not applicable)	16.7	14.3	17.6	5.9

Statistical analyses

Statistical analysis title	MK-3655 50 mg vs Placebo
Comparison groups	MK-3655 50 mg v Placebo

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3504 [1]
Method	Miettinen and Nurminen's method
Parameter estimate	Difference in Percentages
Point estimate	10.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.4
upper limit	35.1

Notes:

[1] - Stratified by concurrent diagnosis of T2DM at the time of randomization and fibrosis score and using Cochran-Mantel-Haenszel weighting scheme

Statistical analysis title	MK-3655 100 mg vs Placebo
Comparison groups	MK-3655 100 mg v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.373 [2]
Method	Miettinen and Nurminen's method
Parameter estimate	Difference in Percentages
Point estimate	9.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.6
upper limit	32.1

Notes:

[2] - Stratified by concurrent diagnosis of T2DM at the time of randomization and fibrosis score and using Cochran-Mantel-Haenszel weighting scheme

Statistical analysis title	MK-3655 300 mg vs Placebo
Comparison groups	MK-3655 300 mg v Placebo
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1428 [3]
Method	Miettinen and Nurminen's method
Parameter estimate	Difference in Percentages
Point estimate	15.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.5
upper limit	42.3

Notes:

[3] - Stratified by concurrent diagnosis of T2DM at the time of randomization and fibrosis score and using Cochran-Mantel-Haenszel weighting scheme

Primary: Percentage of Participants Who Experienced an Adverse Event (AE)

End point title	Percentage of Participants Who Experienced an Adverse Event (AE)[4]

End point description:

An AE was defined as any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it was considered related to the medical treatment or procedure, that occurred during the course of the study. Analysis population was the All Participants as Treated (APaT) population, which included all randomized participants who received at least 1 injection of study intervention.

End point type	Primary

End point timeframe:

Up to 56 weeks

Notes:

[4] - 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 endpoint

End point values	MK-3655 50 mg	MK-3655 100 mg	MK-3655 300 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45	47	46	44
Units: Percentage of Participants				
number (not applicable)	73.3	70.2	76.1	77.3

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Discontinuing Study Medication Due to an AE

End point title	Percentage of Participants Discontinuing Study Medication Due to an AE[5]

End point description:

An AE was defined as any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it was considered related to the medical treatment or procedure, that occurred during the course of the study. Analysis population was the APaT, which included all randomized participants who received at least 1 injection of study intervention.

End point type	Primary

End point timeframe:

Up to 52 weeks

Notes:

[5] - 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 endpoint

End point values	MK-3655 50 mg	MK-3655 100 mg	MK-3655 300 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45	47	46	44
Units: Percentage of Participants				
number (not applicable)	2.2	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Percent Relative Reduction from Baseline in Liver Fat Content (LFC) After 24 weeks

End point title	Mean Percent Relative Reduction from Baseline in Liver Fat Content (LFC) After 24 weeks

End point description:

LFC % was measured by Magnetic Resonance Imaging-Estimated Proton Density Fat Fraction (MRI-PDFF) and evaluated by BICR. MRI-PDFF is a highly accurate noninvasive measure of the proportion of fat content of a tissue. Analysis population was the FAS, which consisted of all randomized participants who had at least 1 injection of study intervention and had at least 1 assessment.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	MK-3655 50 mg	MK-3655 100 mg	MK-3655 300 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33	36	37	31
Units: Percentage Change				
least squares mean (confidence interval 95%)	30.1 (17.5 to 42.7)	30.0 (18.2 to 41.8)	37.2 (25.5 to 48.8)	11.0 (-0.9 to 23.0)

Statistical analyses

Statistical analysis title	MK-3655 50 mg vs Placebo
Comparison groups	MK-3655 50 mg v Placebo
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in Least Square (LS) Means
Point estimate	19.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.7
upper limit	36.4

Statistical analysis title	MK-3655 300 mg vs Placebo
Comparison groups	MK-3655 300 mg v Placebo

Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in LS Means
Point estimate	26.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.5
upper limit	42.8

Statistical analysis title	MK-3655 100 mg vs Placebo
Comparison groups	MK-3655 100 mg v Placebo
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in LS Means
Point estimate	19
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.2
upper limit	35.8

Secondary: Percentage of Participants With ≥1 Stage Improvement in Fibrosis Without Worsening of Steatohepatitis Assessed With the NASH CRN Scoring System After 52 Weeks

End point title	Percentage of Participants With ≥1 Stage Improvement in Fibrosis Without Worsening of Steatohepatitis Assessed With the NASH CRN Scoring System After 52 Weeks

End point description:

Participants evaluated with the NASH CRN scoring system with BICR with ≥1 stage improvement in fibrosis without worsening of steatohepatitis defined as no increase in the ballooning, inflammation, or steatosis scores. Analysis population was the FAS, which consisted of all randomized participants who had at least 1 injection of study intervention and had at least 1 assessment.

End point type	Secondary

End point timeframe:

Week 52

End point values	MK-3655 50 mg	MK-3655 100 mg	MK-3655 300 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	21	17	17
Units: Percentage of Participants				
number (not applicable)	22.2	38.1	29.4	17.6

Statistical analyses

Statistical analysis title	MK-3655 50 mg vs Placebo
Comparison groups	MK-3655 50 mg v Placebo
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8978 [6]
Method	Miettinen and Nurminen's method
Parameter estimate	Difference in Percentages
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.5
upper limit	30.3

Notes:

[6] - Stratified by concurrent diagnosis of T2DM at the time of randomization and fibrosis score and using Cochran-Mantel-Haenszel weighting scheme

Statistical analysis title	MK-3655 300 mg vs Placebo
Comparison groups	MK-3655 300 mg v Placebo
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5636 [7]
Method	Miettinen and Nurminen's method
Parameter estimate	Difference in Percentages
Point estimate	8.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.1
upper limit	38.5

Notes:

[7] - Stratified by concurrent diagnosis of T2DM at the time of randomization and fibrosis score and using Cochran-Mantel-Haenszel weighting scheme

Statistical analysis title	MK-3655 100 mg vs Placebo
Comparison groups	MK-3655 100 mg v Placebo

Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1869 [8]
Method	Miettinen and Nurminen's method
Parameter estimate	Difference in Parentages
Point estimate	20
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.6
upper limit	46.4

Notes:

[8] - Stratified by concurrent diagnosis of T2DM at the time of randomization and fibrosis score and using Cochran-Mantel-Haenszel weighting scheme

Secondary: Percentage of Participants with ≥2 Point Improvement in NAS with ≥1 Point Improvement in Inflammation or Ballooning without Worsening of Fibrosis by Histology (Evaluated by BICR) after 52 weeks

End point title	Percentage of Participants with ≥2 Point Improvement in NAS with ≥1 Point Improvement in Inflammation or Ballooning without Worsening of Fibrosis by Histology (Evaluated by BICR) after 52 weeks

End point description:

Participants with ≥2 point improvement in the NAS with ≥1 point improvement in inflammation or ballooning without worsening of fibrosis assessed with the NASH CRN scoring system (evaluated by BICR). The NAS was calculated as the unweighted sum of the scores and ranges from 0-8 (highest activity). Analysis population was the FAS, which consisted of all randomized participants who had at least 1 injection of study intervention and had at least 1 assessment.

End point type	Secondary

End point timeframe:

Week 52

End point values	MK-3655 50 mg	MK-3655 100 mg	MK-3655 300 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	21	17	17
Units: Percentage of Participants				
number (not applicable)	33.3	47.6	35.3	29.4

Statistical analyses

Statistical analysis title	MK-3655 50 mg vs Placebo
Comparison groups	MK-3655 50 mg v Placebo

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9174 [9]
Method	Miettinen and Nurminen's method
Parameter estimate	Difference in Percentages
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.6
upper limit	32.6

Notes:

[9] - Stratified by concurrent diagnosis of T2DM at the time of randomization and fibrosis score and using Cochran-Mantel-Haenszel weighting scheme

Statistical analysis title	MK-3655 300 mg vs Placebo
Comparison groups	MK-3655 300 mg v Placebo
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7586 [10]
Method	Miettinen and Nurminen's method
Parameter estimate	Difference in Percentages
Point estimate	5.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.7
upper limit	37.3

Notes:

[10] - Stratified by concurrent diagnosis of T2DM at the time of randomization and fibrosis score and using Cochran-Mantel-Haenszel weighting scheme

Statistical analysis title	MK-3655 100 mg vs Placebo
Comparison groups	MK-3655 100 mg v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.272 [11]
Method	Miettinen and Nurminen's method
Parameter estimate	Difference in Percentages
Point estimate	18.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.5
upper limit	47.1

Notes:

[11] - Stratified by concurrent diagnosis of T2DM at the time of randomization and fibrosis score and using Cochran-Mantel-Haenszel weighting scheme

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 64 weeks

Adverse event reporting additional description:

All-cause mortality population included all enrolled participants. Serious Adverse Events and non-serious AEs population included all participants who received at least 1 dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	MK-3655 50 mg
Reporting group description: -	
Reporting group title	MK-3655 100 mg
Reporting group description: -	
Reporting group title	MK-3655 300 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	MK-3655 50 mg	MK-3655 100 mg	MK-3655 300 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 45 (2.22%)	1 / 47 (2.13%)	1 / 46 (2.17%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Forearm fracture			
subjects affected / exposed	0 / 45 (0.00%)	0 / 47 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Sinoatrial block			
subjects affected / exposed	0 / 45 (0.00%)	0 / 47 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			

subjects affected / exposed	0 / 45 (0.00%)	0 / 47 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 45 (0.00%)	0 / 47 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 45 (0.00%)	0 / 47 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 45 (0.00%)	0 / 47 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 45 (0.00%)	0 / 47 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	0 / 45 (0.00%)	0 / 47 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 45 (0.00%)	0 / 47 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus bladder			
subjects affected / exposed	0 / 45 (0.00%)	1 / 47 (2.13%)	0 / 46 (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

Nephrolithiasis			
subjects affected / exposed	0 / 45 (0.00%)	0 / 47 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19 pneumonia			
subjects affected / exposed	1 / 45 (2.22%)	0 / 47 (0.00%)	0 / 46 (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
Diverticulitis			
subjects affected / exposed	0 / 45 (0.00%)	0 / 47 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 45 (0.00%)	0 / 47 (0.00%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 44 (18.18%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Forearm fracture			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Sinoatrial block			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Non-cardiac chest pain			

subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rectal haemorrhage			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Large intestine polyp			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Calculus bladder			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Nephrolithiasis			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
COVID-19 pneumonia			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis acute			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	MK-3655 50 mg	MK-3655 100 mg	MK-3655 300 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 45 (42.22%)	26 / 47 (55.32%)	27 / 46 (58.70%)
Investigations			
Weight increased			
subjects affected / exposed	1 / 45 (2.22%)	1 / 47 (2.13%)	3 / 46 (6.52%)
occurrences (all)	1	1	3
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 45 (4.44%)	6 / 47 (12.77%)	6 / 46 (13.04%)
occurrences (all)	2	8	7
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 45 (4.44%)	1 / 47 (2.13%)	5 / 46 (10.87%)
occurrences (all)	2	1	6
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	2 / 45 (4.44%)	2 / 47 (4.26%)	2 / 46 (4.35%)
occurrences (all)	4	2	2
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 45 (2.22%)	0 / 47 (0.00%)	3 / 46 (6.52%)
occurrences (all)	1	0	3
Diarrhoea			
subjects affected / exposed	4 / 45 (8.89%)	7 / 47 (14.89%)	5 / 46 (10.87%)
occurrences (all)	5	7	5
Nausea			
subjects affected / exposed	2 / 45 (4.44%)	3 / 47 (6.38%)	1 / 46 (2.17%)
occurrences (all)	2	3	2
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 45 (0.00%)	1 / 47 (2.13%)	1 / 46 (2.17%)
occurrences (all)	0	1	1
Back pain			
subjects affected / exposed	1 / 45 (2.22%)	3 / 47 (6.38%)	4 / 46 (8.70%)
occurrences (all)	2	3	6
Arthralgia			
subjects affected / exposed	1 / 45 (2.22%)	1 / 47 (2.13%)	7 / 46 (15.22%)
occurrences (all)	1	1	11
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	3 / 45 (6.67%)	2 / 47 (4.26%)	1 / 46 (2.17%)
occurrences (all)	3	2	1
Nasopharyngitis			
subjects affected / exposed	2 / 45 (4.44%)	4 / 47 (8.51%)	2 / 46 (4.35%)
occurrences (all)	2	6	2
Influenza			
subjects affected / exposed	1 / 45 (2.22%)	3 / 47 (6.38%)	0 / 46 (0.00%)
occurrences (all)	1	3	0
COVID-19			
subjects affected / exposed	4 / 45 (8.89%)	9 / 47 (19.15%)	5 / 46 (10.87%)
occurrences (all)	4	11	6

Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	2 / 45 (4.44%)	5 / 47 (10.64%)	4 / 46 (8.70%)
occurrences (all)	2	5	4
Decreased appetite			
subjects affected / exposed	3 / 45 (6.67%)	1 / 47 (2.13%)	0 / 46 (0.00%)
occurrences (all)	3	1	0

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 44 (47.73%)		
Investigations			
Weight increased			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	4		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 44 (9.09%)		
occurrences (all)	5		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 44 (4.55%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	5		
Nausea			
subjects affected / exposed	4 / 44 (9.09%)		
occurrences (all)	4		
Musculoskeletal and connective tissue			

disorders			
Pain in extremity			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	4		
Back pain			
subjects affected / exposed	3 / 44 (6.82%)		
occurrences (all)	4		
Arthralgia			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 44 (2.27%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
COVID-19			
subjects affected / exposed	5 / 44 (11.36%)		
occurrences (all)	5		
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		
Decreased appetite			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 March 2021	Amendment 1: Data Monitoring Committee (DMC) was changed from the Sponsor’s siDMC to an eDMC.
24 June 2021	Amendment 2: Enhanced operational efficiency of the study
30 November 2021	Amendment 3: Expanded the participant population to include premenopausal women
24 June 2022	Amendment 4: Modified the Interim Analysis (IA) futility criterion
07 September 2022	Amendment 5: Harmonized follow-up safety monitoring of all study participants through Week 64

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported