Clinical trial results:
A Multicenter, Open-label Study to Evaluate the Safety and Diagnostic Efficacy of Mangoral in Patients with Known or Suspected Focal Liver Lesions and Severe Renal Impairment

Summary

EudraCT number	2019-001599-12
Trial protocol	DE SE PL IT
Global end of trial date	17 February 2023

Results information

Result version number	v1 (current)
This version publication date	22 December 2024
First version publication date	22 December 2024

Trial information

Trial identification

Sponsor protocol code	ASC-Man-P016

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04119843
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ascelia Pharma AB
Sponsor organisation address	Hyllie Boulevard 34, Malmö, Sweden, 215 32
Public contact	Jennie Wilborgsson, Ascelia Pharma AB, +46 700721144, jennie.wilborgsson@ascelia.com
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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	17 February 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 February 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the safety and efficacy of mangoral (800 mg MnCl2 4H2O) in participants with known or suspected focal liver lesions and severe renal impairment.

Protection of trial subjects:

This study was conducted in compliance with Good Clinical Practice, including the archiving of essential documents. An Independent Data Safety Monitoring Board also reviewed all safety data available once 30 participants had completed the third follow-up visit (5 days after the administration of mangoral), and made recommendations to the Sponsor.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 February 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	Germany: 9
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	Mexico: 7
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Russian Federation: 13
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	Türkiye: 12
Country: Number of subjects enrolled	United States: 19
Worldwide total number of subjects	87
EEA total number of subjects	34

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)	42
From 65 to 84 years	45
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 87 participants were enrolled in 32 study sites in Europe, Asia, North America, and South America between February 2020 and February 2023.

Pre-assignment

Screening details:

The study consisted of:
• Screening Period (Day -28 to Day -1)
• Baseline Period (Day -1 to Day 0, i.e., within 24 hours of mangoral administration)
• Day of magnetic resonance imaging (MRI) (Day 0) included intake of mangoral and mangoral-enhanced liver MRI
• Follow-up visits following contrast administration (up to Day 7).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Mangoral

Arm description:

All participants received a single oral dose of mangoral (800 mg manganese [II] chloride tetrahydrate [MnCl2 4H2O]). Mangoral is a novel manganese-based contrast agent for liver MRI.

Unenhanced MRI of the liver was performed during the Baseline Period, i.e., either on the day prior to the mangoral-enhanced MRI or predose on the same day as the mangoral-enhanced MRI. Mangoral-enhanced MRI of the liver was performed 4 (±1) hours after investigational medicinal product (IMP) administration. Each unenhanced and each mangoral-enhanced liver MRI examination will consist of axial T1- and T2-weighted image sequences and a diffusion-weighted imaging (DWI) sequence.

Arm type	Experimental
Investigational medicinal product name	Mangoral
Investigational medicinal product code	
Other name	Orviglance, CMC-001, ACE-MBCA
Pharmaceutical forms	Powder for oral solution in sachet
Routes of administration	Oral use

Dosage and administration details:

800 mg manganese chloride (II) tetrahydrate, 500 mg L-alanine, and 800 IU vitamin D3.

Number of subjects in period 1	Mangoral
Started	87
Underwent Unenhanced MRI	85
Underwent Mangoral-enhanced MRI	85
Completed	83
Not completed	4
Adverse event, non-fatal	3
Death	1

Baseline characteristics

Reporting groups	
Reporting group title	Mangoral

Reporting group description:

All participants received a single oral dose of mangoral (800 mg manganese [II] chloride tetrahydrate [MnCl2 4H2O]). Mangoral is a novel manganese-based contrast agent for liver MRI.

Unenhanced MRI of the liver was performed during the Baseline Period, i.e., either on the day prior to the mangoral-enhanced MRI or predose on the same day as the mangoral-enhanced MRI. Mangoral-enhanced MRI of the liver was performed 4 (±1) hours after investigational medicinal product (IMP) administration. Each unenhanced and each mangoral-enhanced liver MRI examination will consist of axial T1- and T2-weighted image sequences and a diffusion-weighted imaging (DWI) sequence.

Reporting group values	Mangoral	Total	
Number of subjects	87	87	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	64.7		
standard deviation	± 11.63	-	
Gender categorical Units: Subjects			
Female	36	36	
Male	51	51	
Ethnicity Units: Subjects			
Hispanic or Latino	11	11	
Not Hispanic or Latino	28	28	
Unknown or Not Reported	48	48	
Race Units: Subjects			
White	28	28	
Black or African American	5	5	
American Indian or Alaska Native	1	1	
Other	6	6	
Unknown or Not Reported	47	47	

End points

End points reporting groups

Reporting group title	Mangoral

Reporting group description:

All participants received a single oral dose of mangoral (800 mg manganese [II] chloride tetrahydrate [MnCl2 4H2O]). Mangoral is a novel manganese-based contrast agent for liver MRI.

Unenhanced MRI of the liver was performed during the Baseline Period, i.e., either on the day prior to the mangoral-enhanced MRI or predose on the same day as the mangoral-enhanced MRI. Mangoral-enhanced MRI of the liver was performed 4 (±1) hours after investigational medicinal product (IMP) administration. Each unenhanced and each mangoral-enhanced liver MRI examination will consist of axial T1- and T2-weighted image sequences and a diffusion-weighted imaging (DWI) sequence.

Subject analysis set title	Unenhanced MRI
Subject analysis set type	Full analysis

Subject analysis set description:

All participants undertook an unenhanced MRI examination of the liver during the Baseline Period (Day -1 to Day 0, i.e., within 24 hours of mangoral administration).

Unenhanced MRI was defined as the reading of the pre-mangoral, unenhanced MRI only.

Subject analysis set title	Mangoral-enhanced MRI
Subject analysis set type	Full analysis

Subject analysis set description:

All participants undertook an unenhanced MRI examination of the liver during the Baseline Period (Day -1 to Day 0, i.e., within 24 hours of mangoral administration).

On the day of MRI (Day 0), all participants received a single oral dose of mangoral (800 mg) after a fast of at least 4 hours and undertook a mangoral-enhanced MRI examination of the liver 4 [±1] hours after mangoral administration.

Mangoral-enhanced MRI was defined as the reading of the mangoral enhanced MRI only.

Subject analysis set title	Combined MRI
Subject analysis set type	Full analysis

Subject analysis set description:

All participants undertook an unenhanced MRI examination of the liver during the Baseline Period (Day -1 to Day 0, i.e., within 24 hours of mangoral administration).

On the day of MRI (Day 0), all participants received a single oral dose of mangoral equivalent to 800 mg MnCl2 4H2O after a fast of at least 4 hours and undertook a mangoral-enhanced MRI examination of the liver (paired with unenhanced MRI; combined MRI) 4 (±1) hours after mangoral administration.

Combined MRI was defined as the paired, simultaneous reading of both unenhanced and mangoral-enhanced MRIs.

Primary: Co-primary Endpoint: Lesion Border Delineation in Combined MRI Compared to Unenhanced MRI

End point title	Co-primary Endpoint: Lesion Border Delineation in Combined MRI Compared to Unenhanced MRI

End point description:

Visualization of focal liver lesions was measured by 2 co-primary variables: 'lesion border delineation' and 'lesion contrast' compared to liver background. Qualitative assessment determined on the 4-point scales for up to 15 lesions per participant. Each lesion was assessed for lesion border delineation from 1 (poor: lesion border is poorly distinct) to 4 (excellent: lesion border is sharply and clearly distinct). Central reading sessions were undertaken by 3 independent, blinded readers.

Full Analysis Set (FAS): All participants of the Safety Population who received the IMP and for whom the primary efficacy variable was assessable, i.e. all unenhanced / enhanced liver MRI images are assessable.

End point type	Primary

End point timeframe:

Unenhanced MRI: Baseline Period (Day -1 to Day 0); combined MRI: Baseline Period (Day -1 to Day 0) and 4 hours after mangoral administration on Day 0

End point values	Unenhanced MRI	Combined MRI		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	85		
Units: score on a scale				
arithmetic mean (standard deviation)				
Reader 1 (N = 61, 61)	2.51 (± 0.815)	3.46 (± 0.861)		
Reader 2 (N = 53, 53)	3.00 (± 0.952)	3.80 (± 0.607)		
Reader 3 (N = 61, 61)	2.31 (± 0.847)	2.97 (± 0.782)		

Statistical analyses

Statistical analysis title	Reader 1: combined MRI versus (vs.) unenhanced MRI

Statistical analysis description:

Reader success for the primary analysis was achieved if the reading results of a reader demonstrated superiority of combined MRI versus unenhanced MRI for both lesion border delineation and lesion contrast. The acceptance by two out of three readers was considered to be a successful demonstration of efficacy in the study.

Positive changes in lesion border delineation (combined MRI compared to the unenhanced MRI) represents a better outcome.

Comparison groups	Unenhanced MRI v Combined MRI
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.001 [2]
Method	t-test, 1-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.743
upper limit	1.165
Variability estimate	Standard deviation
Dispersion value	0.824

Notes:

[1] - Actual number subjects in this analysis: 61.

[2] - p-values show a one-sided t-test with a significance level of 0.025.

Statistical analysis title	Reader 2: combined MRI vs. unenhanced MRI

Statistical analysis description:

Reader success for the primary analysis was achieved if the reading results of a reader demonstrated superiority of combined MRI versus unenhanced MRI for both lesion border delineation and lesion contrast. The acceptance by two out of three readers was considered to be a successful demonstration of efficacy in the study.

Positive changes in lesion border delineation (combined MRI compared to the unenhanced MRI) represents a better outcome.

Comparison groups	Unenhanced MRI v Combined MRI
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.001 [4]
Method	t-test, 1-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.552
upper limit	1.043
Variability estimate	Standard deviation
Dispersion value	0.892

Notes:

[3] - Actual number subjects in this analysis: 53.

[4] - p-values show a one-sided t-test with a significance level of 0.025.

Statistical analysis title	Reader 3: combined MRI vs. unenhanced MRI

Statistical analysis description:

Reader success for the primary analysis was achieved if the reading results of a reader demonstrated superiority of combined MRI versus unenhanced MRI for both lesion border delineation and lesion contrast. The acceptance by two out of three readers was considered to be a successful demonstration of efficacy in the study.

Positive changes in lesion border delineation (combined MRI compared to the unenhanced MRI) represents a better outcome.

Comparison groups	Unenhanced MRI v Combined MRI
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.001 [6]
Method	t-test, 1-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.494
upper limit	0.813
Variability estimate	Standard deviation
Dispersion value	0.622

Notes:

[5] - Actual number subjects in this analysis: 61.

[6] - p-values show a one-sided t-test with a significance level of 0.025.

Primary: Co-primary Endpoint: Lesion Contrast in Combined MRI Compared to Unenhanced MRI

End point title	Co-primary Endpoint: Lesion Contrast in Combined MRI Compared to Unenhanced MRI

End point description:

Visualization of focal liver lesions was measured by 2 co-primary variables: 'lesion border delineation' and 'lesion contrast' compared to liver background. Qualitative assessment determined on the 4-point scales for up to 15 lesions per participant. Each lesion was assessed for lesion contrast from 1 (poor: difference in signal intensity between the lesion and the surrounding normal liver tissue is poor) to 4 (excellent: difference in signal intensity between the lesion and the surrounding liver is marked). Central reading sessions were undertaken by 3 independent, blinded readers.

The scores were calculated for each participant by summing the individual lesion scores and calculating the mean. The total score could range from 1 to 4 for each participant with higher scores representing a better outcome.

FAS: All participants of the Safety Population who received the IMP and for whom the primary efficacy variable was assessable.

End point type	Primary

End point timeframe:

Unenhanced MRI: Baseline Period (Day -1 to Day 0); combined MRI: Baseline Period (Day -1 to Day 0) and 4 hours after mangoral administration on Day 0

End point values	Unenhanced MRI	Combined MRI		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	85		
Units: score on a scale				
arithmetic mean (standard deviation)				
Reader 1 (N = 61, 61)	2.49 (± 0.813)	3.47 (± 0.844)		
Reader 2 (N = 53, 53)	2.84 (± 0.926)	3.86 (± 0.417)		
Reader 3 (N = 61, 61)	2.51 (± 0.919)	3.33 (± 0.684)		

Statistical analyses

Statistical analysis title	Reader 1: combined MRI vs. unenhanced MRI

Statistical analysis description:

Reader success for the primary endpoint was achieved if the reading results of a reader demonstrated superiority of combined MRI versus unenhanced MRI for both lesion border delineation and lesion contrast. The acceptance by two out of three readers was considered to be a successful demonstration of efficacy in the study.

Positive changes in lesion contrast (combined MRI compared to the unenhanced MRI) represents a better outcome.

Comparison groups	Unenhanced MRI v Combined MRI
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	< 0.001 [8]
Method	t-test, 1-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.98

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.759
upper limit	1.196
Variability estimate	Standard deviation
Dispersion value	0.853

Notes:

[7] - Actual number subjects in this analysis: 61.

[8] - p-values show a one-sided t-test with a significance level of 0.025.

Statistical analysis title	Reader 2: combined MRI vs. unenhanced MRI

Statistical analysis description:

Reader success for the primary endpoint was achieved if the reading results of a reader demonstrated superiority of combined MRI versus unenhanced MRI for both lesion border delineation and lesion contrast. The acceptance by two out of three readers was considered to be a successful demonstration of efficacy in the study.

Positive changes in lesion contrast (combined MRI compared to the unenhanced MRI) represents a better outcome.

Comparison groups	Unenhanced MRI v Combined MRI
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	< 0.001 [10]
Method	t-test, 1-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.766
upper limit	1.267
Variability estimate	Standard deviation
Dispersion value	0.909

Notes:

[9] - Actual number subjects in this analysis: 53.

[10] - p-values show a one-sided t-test with a significance level of 0.025.

Statistical analysis title	Reader 3: combined MRI vs. unenhanced MRI

Statistical analysis description:

Reader success for the primary endpoint was achieved if the reading results of a reader demonstrated superiority of combined MRI versus unenhanced MRI for both lesion border delineation and lesion contrast. The acceptance by two out of three readers was considered to be a successful demonstration of efficacy in the study.

Positive changes in lesion contrast (combined MRI compared to the unenhanced MRI) represents a better outcome.

Comparison groups	Unenhanced MRI v Combined MRI

Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	< 0.001 [12]
Method	t-test, 1-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.638
upper limit	0.985
Variability estimate	Standard deviation
Dispersion value	0.678

Notes:

[11] - Actual number subjects in this analysis: 61.

[12] - p-values show a one-sided t-test with a significance level of 0.025.

Secondary: Number of Lesions Detected by Each MRI Method

End point title	Number of Lesions Detected by Each MRI Method

End point description:

Assessments of unenhanced MRI, mangoral-enhanced MRI, and combined MRI for detection of lesions were undertaken by on-site readers (assessing participants at their own site) and during central reading sessions by 3 independent, blinded readers.

FAS: All participants of the Safety Population who received the IMP and for whom the primary efficacy variable was assessable, i.e. all unenhanced / enhanced liver MRI images are assessable.

End point type	Secondary

End point timeframe:

Unenhanced MRI: Baseline Period (Day -1 to Day 0); mangoral-enhanced MRI: 4 hours after mangoral administration on Day 0; and combined MRI: Baseline Period (Day -1 to Day 0) and 4 hours after mangoral administration on Day 0

End point values	Unenhanced MRI	Mangoral-enhanced MRI	Combined MRI	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	85	85	85[13]	
Units: lesions				
arithmetic mean (standard deviation)				
On-site Readers	5.7 (± 9.07)	6.2 (± 9.35)	6.4 (± 9.57)	
Reader 1	3.5 (± 5.18)	4.3 (± 5.39)	4.2 (± 5.19)	
Reader 2	3.1 (± 5.07)	3.6 (± 5.34)	3.2 (± 4.85)	
Reader 3	4.1 (± 5.58)	4.5 (± 5.55)	4.3 (± 5.59)	

Notes:

[13] - Readers 1 and 2 N = 84.

Statistical analyses

No statistical analyses for this end point

Secondary: Lesion Border Delineation in Mangoral-enhanced MRI Compared to

Unenhanced MRI

End point title	Lesion Border Delineation in Mangoral-enhanced MRI Compared to Unenhanced MRI

End point description:

Visualization of focal liver lesions was measured by variables: 'lesion border delineation' and 'lesion contrast' compared to liver background. Qualitative assessment determined on the 4-point scales for up to 15 lesions per participant. Each lesion was assessed for lesion border delineation from 1 (poor: lesion border is poorly distinct) to 4 (excellent: lesion border is sharply and clearly distinct). Central reading sessions were undertaken by 3 independent, blinded readers.

The scores were calculated for each participant by summing the individual lesion scores and calculating the mean. The total score could range from 1 to 4 for each participant with higher scores representing a better outcome.

FAS: All participants of the Safety Population who received the IMP and for whom the primary efficacy variable was assessable, i.e. all unenhanced / enhanced liver MRI images are assessable.

End point type	Secondary

End point timeframe:

Unenhanced MRI: Baseline Period (Day -1 to Day 0); mangoral-enhanced MRI: 4 hours after mangoral administration on Day 0

End point values	Unenhanced MRI	Mangoral-enhanced MRI		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	85		
Units: score on a scale				
arithmetic mean (standard deviation)				
Reader 1 (N = 60, 60)	2.57 (± 0.783)	3.34 (± 0.814)		
Reader 2 (N = 52, 52)	2.95 (± 0.986)	3.71 (± 0.647)		
Reader 3 (N = 59, 59)	2.27 (± 0.854)	2.86 (± 0.881)		

Statistical analyses

Statistical analysis title	Reader 1: mangoral-enhanced MRI vs. unenhanced MRI

Statistical analysis description:

Reader success was achieved if the reading results of a reader demonstrated superiority of mangoral-enhanced MRI versus unenhanced MRI for both lesion border delineation and lesion contrast. The acceptance by two out of three readers was considered to be a successful demonstration of efficacy in the study.

Positive changes in lesion border delineation (mangoral-enhanced MRI compared to the unenhanced MRI) represents a better outcome.

Comparison groups	Unenhanced MRI v Mangoral-enhanced MRI
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	< 0.001 [15]
Method	t-test, 1-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.76

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.555
upper limit	0.971
Variability estimate	Standard deviation
Dispersion value	0.805

Notes:

[14] - Actual number subjects in this analysis: 60.

[15] - p-values show a one-sided t-test with a significance level of 0.025.

Statistical analysis title	Reader 2: mangoral-enhanced MRI vs. unenhanced MRI

Statistical analysis description:

Reader success was achieved if the reading results of a reader demonstrated superiority of mangoral-enhanced MRI versus unenhanced MRI for both lesion border delineation and lesion contrast. The acceptance by two out of three readers was considered to be a successful demonstration of efficacy in the study.

Positive changes in lesion border delineation (mangoral-enhanced MRI compared to the unenhanced MRI) represents a better outcome.

Comparison groups	Unenhanced MRI v Mangoral-enhanced MRI
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	< 0.001 [17]
Method	t-test, 1-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.464
upper limit	1.054
Variability estimate	Standard deviation
Dispersion value	1.059

Notes:

[16] - Actual number subjects in this analysis: 52.

[17] - p-values show a one-sided t-test with a significance level of 0.025.

Statistical analysis title	Reader 3: mangoral-enhanced MRI vs. unenhanced MRI

Statistical analysis description:

Reader success was achieved if the reading results of a reader demonstrated superiority of mangoral-enhanced MRI versus unenhanced MRI for both lesion border delineation and lesion contrast. The acceptance by two out of three readers was considered to be a successful demonstration of efficacy in the study.

Positive changes in lesion border delineation (mangoral-enhanced MRI compared to the unenhanced MRI) represents a better outcome.

Comparison groups	Unenhanced MRI v Mangoral-enhanced MRI

Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	< 0.001 [19]
Method	t-test, 1-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.429
upper limit	0.747
Variability estimate	Standard deviation
Dispersion value	0.609

Notes:

[18] - Actual number subjects in this analysis: 59.

[19] - p-values show a one-sided t-test with a significance level of 0.025.

Secondary: Lesion Contrast in Mangoral-enhanced MRI Compared to Unenhanced MRI

End point title	Lesion Contrast in Mangoral-enhanced MRI Compared to Unenhanced MRI

End point description:

Visualization of focal liver lesions was measured by variables: 'lesion border delineation' and 'lesion contrast' compared to liver background. Qualitative assessment determined on the 4-point scales for up to 15 lesions per participant. Each lesion was assessed for lesion contrast from 1 (poor: difference in signal intensity between the lesion and the surrounding normal liver tissue is poor) to 4 (excellent: difference in signal intensity between the lesion and the surrounding liver is marked). Central reading sessions were undertaken by 3 independent, blinded readers.

The scores were calculated for each participant by summing the individual lesion scores and calculating the mean. The total score could range from 1 to 4 for each participant with higher scores representing a better outcome.

FAS: All participants of the Safety Population who received the IMP and for whom the primary efficacy variable was assessable, i.e. all unenhanced / enhanced liver MRI images are assessable.

End point type	Secondary

End point timeframe:

Unenhanced MRI: Baseline Period (Day -1 to Day 0); mangoral-enhanced MRI: 4 hours after mangoral administration on Day 0

End point values	Unenhanced MRI	Mangoral-enhanced MRI		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	85		
Units: score on a scale				
arithmetic mean (standard deviation)				
Reader 1 (N = 60, 60)	2.57 (± 0.787)	3.52 (± 0.735)		
Reader 2 (N = 52, 52)	2.80 (± 0.940)	3.53 (± 0.816)		
Reader 3 (N = 59, 59)	2.46 (± 0.933)	3.18 (± 0.882)		

Statistical analyses

Statistical analysis title	Reader 1: mangoral-enhanced MRI vs. unenhanced MRI

Statistical analysis description:

Reader success was achieved if the reading results of a reader demonstrated superiority of mangoral-enhanced MRI versus unenhanced MRI for both lesion border delineation and lesion contrast. The acceptance by two out of three readers was considered to be a successful demonstration of efficacy in the study.

Positive changes in lesion contrast (mangoral-enhanced MRI compared to the unenhanced MRI) represents a better outcome.

Comparison groups	Unenhanced MRI v Mangoral-enhanced MRI
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	< 0.001 [21]
Method	t-test, 1-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.726
upper limit	1.166
Variability estimate	Standard deviation
Dispersion value	0.852

Notes:

[20] - Actual number subjects in this analysis: 60.

[21] - p-values show a one-sided t-test with a significance level of 0.025.

Statistical analysis title	Reader 2: mangoral-enhanced MRI vs. unenhanced MRI

Statistical analysis description:

Reader success was achieved if the reading results of a reader demonstrated superiority of mangoral-enhanced MRI versus unenhanced MRI for both lesion border delineation and lesion contrast. The acceptance by two out of three readers was considered to be a successful demonstration of efficacy in the study.

Positive changes in lesion contrast (mangoral-enhanced MRI compared to the unenhanced MRI) represents a better outcome.

Comparison groups	Unenhanced MRI v Mangoral-enhanced MRI
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[22]
P-value	< 0.001 [23]
Method	t-test, 1-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	1.082
Variability estimate	Standard deviation
Dispersion value	1.261

Notes:

[22] - Actual number subjects in this analysis: 52.

[23] - p-values show a one-sided t-test with a significance level of 0.025.

Statistical analysis title	Reader 3: mangoral-enhanced MRI vs. unenhanced MRI

Statistical analysis description:

Reader success was achieved if the reading results of a reader demonstrated superiority of mangoral-enhanced MRI versus unenhanced MRI for both lesion border delineation and lesion contrast. The acceptance by two out of three readers was considered to be a successful demonstration of efficacy in the study.

Positive changes in lesion contrast (mangoral-enhanced MRI compared to the unenhanced MRI) represents a better outcome.

Comparison groups	Unenhanced MRI v Mangoral-enhanced MRI
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority[24]
P-value	< 0.001 [25]
Method	t-test, 1-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.517
upper limit	0.927
Variability estimate	Standard deviation
Dispersion value	0.786

Notes:

[24] - Actual number subjects in this analysis: 59.

[25] - p-values show a one-sided t-test with a significance level of 0.025.

Secondary: Confidence in Lesion Detection Score

End point title	Confidence in Lesion Detection Score

End point description:

Each lesion was evaluated on a 3-point scale: 1 (lesion is detected with low confidence), 2 (lesion is detected with moderate confidence), 3 (lesion is detected with high confidence). Higher confidence in lesion detection scores represent better outcomes.

Assessments of unenhanced MRI, mangoral-enhanced MRI, and combined MRI for confidence in lesion detection were undertaken by on-site readers (assessing participants are their own site) and during central reading sessions by 3 independent, blinded readers.

FAS: All participants of the Safety Population who received the IMP and for whom the primary efficacy variable was assessable, i.e. all unenhanced / enhanced liver MRI images are assessable.

End point type	Secondary

End point timeframe:

Unenhanced MRI: Baseline Period (Day -1 to Day 0); mangoral-enhanced MRI: 4 hours after mangoral administration on Day 0; and combined MRI: Baseline Period (Day -1 to Day 0) and 4 hours after mangoral administration on Day 0

End point values	Unenhanced MRI	Mangoral-enhanced MRI	Combined MRI	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	85[26]	85[27]	85[28]	
Units: score on a scale				
arithmetic mean (standard deviation)				
On-site Readers (N = 387, 417, 397)	2.5 (± 0.66)	2.8 (± 0.42)	2.8 (± 0.47)	
Reader 1 (N = 301, 362, 350)	2.8 (± 0.54)	2.8 (± 0.53)	2.8 (± 0.57)	
Reader 2 (N = 265, 306, 265)	3.0 (± 0.26)	3.0 (± 0.20)	2.9 (± 0.29)	
Reader 3 (N = 347, 381, 368)	2.8 (± 0.59)	2.9 (± 0.45)	2.9 (± 0.38)	

Notes:

[26] - N values within row titles represent number of lesions included within analysis.

[27] - N values within row titles represent number of lesions included within analysis.

[28] - N values within row titles represent number of lesions included within analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Confidence in Lesion Localization Score

End point title	Confidence in Lesion Localization Score

End point description:

Each lesion was evaluated on a 3-point scale: 1 (lesion is localized to a liver segment with low confidence), 2 (lesion is localized to a liver segment with moderate confidence), 3 (lesion is localized to a liver segment with high confidence).

Assessments of unenhanced MRI, mangoral-enhanced MRI, and combined MRI for confidence in lesion localization were undertaken by on-site readers (assessing participants at their own site) and during central reading sessions by 3 independent, blinded readers.

FAS: All participants of the Safety Population who received the IMP and for whom the primary efficacy variable was assessable, i.e. all unenhanced / enhanced liver MRI images are assessable.

End point type	Secondary

End point timeframe:

Unenhanced MRI: Baseline Period (Day -1 to Day 0); mangoral-enhanced MRI: 4 hours after mangoral administration on Day 0; and combined MRI: Baseline Period (Day -1 to Day 0) and 4 hours after mangoral administration on Day 0

End point values	Unenhanced MRI	Mangoral-enhanced MRI	Combined MRI	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	85[29]	85[30]	85[31]	
Units: score on a scale				
arithmetic mean (standard deviation)				
On-site Readers (N = 387, 417, 397)	2.5 (± 0.65)	2.9 (± 0.42)	2.8 (± 0.49)	
Reader 1 (N = 301, 362, 350)	2.7 (± 0.57)	2.8 (± 0.51)	2.8 (± 0.51)	
Reader 2 (N = 265, 306, 265)	2.9 (± 0.30)	3.0 (± 0.20)	3.0 (± 0.19)	
Reader 3 (N = 347, 381, 368)	2.9 (± 0.33)	2.9 (± 0.26)	3.0 (± 0.17)	

Notes:

[29] - N values within row titles represent number of lesions included within analysis.

[30] - N values within row titles represent number of lesions included within analysis.

[31] - N values within row titles represent number of lesions included within analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Longest Diameter of Largest and Smallest Lesion

End point title	Longest Diameter of Largest and Smallest Lesion

End point description:

Assessments of unenhanced MRI and mangoral-enhanced MRI for lesion dimensions were undertaken during central reading sessions by 3 independent, blinded readers.

FAS: All participants of the Safety Population who received the IMP and for whom the primary efficacy variable was assessable, i.e. all unenhanced / enhanced liver MRI images are assessable.

End point type	Secondary

End point timeframe:

Unenhanced MRI: Baseline Period (Day -1 to Day 0); mangoral-enhanced MRI: 4 hours after mangoral administration on Day 0

End point values	Unenhanced MRI	Mangoral-enhanced MRI		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	85		
Units: mm				
arithmetic mean (standard deviation)				
Smallest Lesion: Reader 1 (N = 63, 69)	23.5 (± 23.75)	21.4 (± 24.20)		
Smallest Lesion: Reader 2 (N = 57, 62)	27.2 (± 25.50)	25.3 (± 26.46)		
Smallest Lesion: Reader 3 (N = 66, 66)	19.8 (± 23.89)	17.0 (± 23.06)		
Largest Lesion: Reader 1 (N = 63, 69)	42.2 (± 32.49)	38.2 (± 29.53)		
Largest Lesion: Reader 2 (N = 57, 62)	44.5 (± 31.49)	47.9 (± 36.03)		
Largest Lesion: Reader 3 (N = 66, 66)	35.5 (± 31.25)	35.2 (± 27.45)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Liver Signal Intensity (SI) Enhancement in Mangoral-enhanced MRI Compared to Unenhanced MRI

End point title	Percentage Liver Signal Intensity (SI) Enhancement in Mangoral-enhanced MRI Compared to Unenhanced MRI

End point description:

Quantitative SI was measured by positioning circular regions of interest in a homogenous area in the liver and the assessed liver lesion on the same image. SI liver was defined as the SI of the liver. Liver SI enhancement (%) = ([SI liver post contrast – SI liver pre contrast] / [SI liver pre contrast]) × 100.

Assessments of unenhanced MRI and mangoral-enhanced MRI for liver SI were undertaken during central reading sessions by the 3 independent, blinded readers.

FAS: All participants of the Safety Population who received the IMP and for whom the primary efficacy variable was assessable, i.e. all unenhanced / enhanced liver MRI images are assessable. As pre-specified in the statistical analysis plan, results are presented for SI enhancement following mangoralenhanced MRI only.

End point type	Secondary

End point timeframe:

Unenhanced MRI: Baseline Period (Day -1 to Day 0); mangoral-enhanced MRI: 4 hours after mangoral administration on Day 0

End point values	Mangoral-enhanced MRI			
Subject group type	Subject analysis set			
Number of subjects analysed	85			
Units: Percentage SI enhancement				
arithmetic mean (standard deviation)				
Reader 1 (N = 73)	72.159 (± 148.2818)			
Reader 2 (N = 83)	59.633 (± 113.7548)			
Reader 3 (N = 85)	61.456 (± 105.3634)			

Statistical analyses

No statistical analyses for this end point

Secondary: Liver-to-lesion Contrast (LLC) in Mangoral-enhanced MRI Compared to Unenhanced MRI

End point title	Liver-to-lesion Contrast (LLC) in Mangoral-enhanced MRI Compared to Unenhanced MRI

End point description:

Quantitative SI was measured by positioning circular regions of interest in a homogenous area in the liver and the assessed liver lesion on the same image. Up to 5 lesions per participant of ≥ 2 cm in diameter were evaluated and these lesions were the same on pre-and post-contrast images. SI lesion was defined as the SI of these lesions. SI liver was defined as the SI of the liver. LLC = (SI liver – SI lesion) / (SI liver + SI lesion). Higher ratio scores represent a better outcome.

Assessments of unenhanced MRI and mangoral-enhanced MRI for LLC ratio were undertaken during central reading sessions by the 3 independent, blinded readers.

FAS: All participants of the Safety Population who received the IMP and for whom the primary efficacy variable was assessable, i.e. all unenhanced / enhanced liver MRI images are assessable.

End point type	Secondary

End point timeframe:

Unenhanced MRI: Baseline Period (Day -1 to Day 0); mangoral-enhanced MRI: 4 hours after mangoral administration on Day 0

End point values	Unenhanced MRI	Mangoral-enhanced MRI		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	85		
Units: ratio				
arithmetic mean (standard deviation)				

Reader 1 (N = 70, 70)	0.143 (± 0.1694)	0.306 (± 0.1816)		
Reader 2 (N = 57, 56)	0.109 (± 0.2739)	0.291 (± 0.2709)		
Reader 3 (N = 47, 47)	0.142 (± 0.1882)	0.331 (± 0.2162)		

Statistical analyses

No statistical analyses for this end point

Secondary: Signal-to-noise Ratio (SNR) in Mangoral-enhanced MRI Compared to Unenhanced MRI

End point title	Signal-to-noise Ratio (SNR) in Mangoral-enhanced MRI Compared to Unenhanced MRI

End point description:

Quantitative SI was measured by positioning circular regions of interest in a homogenous area in the liver and the assessed liver lesion on the same image. Up to 5 lesions per participant of ≥ 2 cm in diameter were evaluated and these lesions were the same on pre-and post-contrast images. SI liver was defined as the SI of the liver. Standard deviation of the background noise was measured using the largest possible rectangular region of interest vertical to the patient's abdomen in the direction of the phase-encoding gradient. SNR = SI liver / standard deviation noise. Higher ratio scores represent a better outcome.

Assessments of unenhanced MRI and mangoral-enhanced MRI for SNR were undertaken during central reading sessions by the 3 independent, blinded readers.

FAS: All participants of the Safety Population who received the IMP and for whom the primary efficacy variable was assessable, i.e. all unenhanced / enhanced liver MRI images are assessable.

End point type	Secondary

End point timeframe:

Unenhanced MRI: Baseline Period (Day -1 to Day 0); mangoral-enhanced MRI: 4 hours after mangoral administration on Day 0

End point values	Unenhanced MRI	Mangoral-enhanced MRI		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	85		
Units: ratio				
arithmetic mean (standard deviation)				
Reader 1 (N = 70, 71)	286.428 (± 581.8717)	322.951 (± 365.1663)		
Reader 2 (N = 78, 79)	226.367 (± 362.3748)	531.223 (± 1175.7566)		
Reader 3 (N = 75, 79)	248.653 (± 508.6403)	419.706 (± 694.8662)		

Statistical analyses

No statistical analyses for this end point

Secondary: Contrast-to-noise Ratio (CNR) in Mangoral-enhanced MRI Compared to Unenhanced MRI

End point title	Contrast-to-noise Ratio (CNR) in Mangoral-enhanced MRI Compared to Unenhanced MRI

End point description:

Quantitative SI was measured by positioning circular regions of interest in a homogenous area in the liver and the assessed liver lesion on the same image. Up to 5 lesions per participant of ≥ 2 cm in diameter were evaluated and these lesions were the same on pre-and post-contrast images. SI lesion was defined as the SI of these lesions. SI liver was defined as the SI of the liver. Standard deviation of the background noise was measured using the largest possible rectangular region of interest vertical to the patient's abdomen in the direction of the phase-encoding gradient. CNR = (SI liver - mean of SI lesion) / standard deviation noise.

Assessments of unenhanced MRI and mangoral-enhanced MRI for CNR were undertaken during central reading sessions by the 3 independent, blinded readers.

FAS: All participants of the Safety Population who received the IMP and for whom the primary efficacy variable was assessable, i.e. all unenhanced / enhanced liver MRI images are assessable.

End point type	Secondary

End point timeframe:

Unenhanced MRI: Baseline Period (Day -1 to Day 0); mangoral-enhanced MRI: 4 hours after mangoral administration on Day 0

End point values	Unenhanced MRI	Mangoral-enhanced MRI		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85[32]	85[33]		
Units: ratio				
arithmetic mean (standard deviation)				
Reader 1 (N = 67, 68)	56.564 (± 197.1474)	137.281 (± 161.1640)		
Reader 2 (N = 53, 54)	33.506 (± 214.2616)	277.270 (± 650.8484)		
Reader 3 (N = 43, 43)	91.019 (± 306.2666)	241.093 (± 510.3520)		

Notes:

[32] - Higher ratio scores represent a better outcome.

[33] - Higher ratio scores represent a better outcome.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Change(s) in Recommended Management Based on Diagnostic Performance of Combined MRI or Mangoral-enhanced MRI Compared to Unenhanced MRI

End point title	Number of Participants With Change(s) in Recommended Management Based on Diagnostic Performance of Combined MRI or Mangoral-enhanced MRI Compared to Unenhanced MRI

End point description:

A participant was considered to have a change in recommended management when compared to unenhanced MRI if recommended management was different following assessment of the combined MRI or mangoral-enhanced MRI, including next steps in management (i.e. chemotherapy, surgery, local ablation procedure, combination therapy, or other [specify]). Recommended patient management from "other" in unenhanced MRI to "other" in combined MRI or mangoral-enhanced MRI was considered not a change regardless of the free text.

Assessments of unenhanced MRI, mangoral-enhanced MRI, and combined MRI for confidence in lesion detection were undertaken by on-site readers (assessing participants at their own site with access to patient records) and during central reading sessions by 3 independent, blinded readers (without access to patient records).

FAS. Results are presented for change in recommended management following combined and mangoral-enhanced MRI.

End point type	Secondary

End point timeframe:

Unenhanced MRI: Baseline Period (Day -1 to Day 0); mangoral-enhanced MRI: 4 hours after mangoral administration on Day 0; and combined MRI: Baseline Period (Day -1 to Day 0) and 4 hours after mangoral administration on Day 0

End point values	Mangoral-enhanced MRI	Combined MRI		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	85	85		
Units: participants				
On-site Readers (N = 83, 83)	4	4		
Reader 1 (N = 85, 84)	19	21		
Reader 2 (N = 85, 84)	27	29		
Reader 3 (N = 85, 85)	19	19		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Day 7

Adverse event reporting additional description:

Safety Population: All participants enrolled in the study (fulfil all inclusion criteria, but none of the exclusion criteria and have been included in the clinical study at Visit 2).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Mangoral

Reporting group description:

All participants received a single oral dose of mangoral (800 mg). Mangoral is a novel manganese-based contrast agent for liver MRI.

Unenhanced MRI of the liver was performed during the Baseline Period, i.e., either on the day prior to the mangoral-enhanced MRI or predose on the same day as the mangoral-enhanced MRI. Mangoral-enhanced MRI of the liver was performed 4 (±1) hours after IMP administration. Each unenhanced and each mangoral-enhanced liver MRI examination will consist of axial T1- and T2-weighted image sequences and a DWI sequence.

Serious adverse events	Mangoral		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 87 (2.30%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

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

Non-serious adverse events	Mangoral		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 87 (47.13%)		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	1		
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 87 (2.30%)		
occurrences (all)	2		
Blood creatine increased			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	5		
Blood creatinine increased			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	1		
Blood glucose decreased			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	1		
Blood glucose increased			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	1		
Blood magnesium decreased			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	1		
Blood potassium decreased			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	1		
Blood pressure increased			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	1		
Blood pressure systolic increased			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	1		
Blood urea increased			

subjects affected / exposed	3 / 87 (3.45%)		
occurrences (all)	7		
Breath sounds abnormal			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	1		
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	1		
Electrocardiogram abnormal			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	1		
Haemoglobin decreased			
subjects affected / exposed	2 / 87 (2.30%)		
occurrences (all)	2		
Heart rate increased			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	1		
International normalised ratio increased			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	1		
Lymphocyte count decreased			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	1		
Neutrophil count increased			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	1		
White blood cells urine positive			
subjects affected / exposed	2 / 87 (2.30%)		
occurrences (all)	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Meningioma			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			

Iatrogenic injury subjects affected / exposed occurrences (all) Procedural vomiting subjects affected / exposed occurrences (all)	 1 / 87 (1.15%) 1 1 / 87 (1.15%) 1		
Vascular disorders Hypotension subjects affected / exposed occurrences (all)	 1 / 87 (1.15%) 1		
Nervous system disorders Paraesthesia subjects affected / exposed occurrences (all)	 1 / 87 (1.15%) 1		
Blood and lymphatic system disorders Leukocytosis subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all) Lymphopenia subjects affected / exposed occurrences (all)	 1 / 87 (1.15%) 1 1 / 87 (1.15%) 1 1 / 87 (1.15%) 1		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Chills subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Pain	 1 / 87 (1.15%) 1 1 / 87 (1.15%) 1 1 / 87 (1.15%) 1		

subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	1		
Abdominal pain			
subjects affected / exposed	2 / 87 (2.30%)		
occurrences (all)	2		
Abdominal pain upper			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	12 / 87 (13.79%)		
occurrences (all)	13		
Dyspepsia			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	14 / 87 (16.09%)		
occurrences (all)	15		
Retching			
subjects affected / exposed	2 / 87 (2.30%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	8 / 87 (9.20%)		
occurrences (all)	8		
Skin and subcutaneous tissue disorders			
Scar pain			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	1		
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	1		
Haematuria			

subjects affected / exposed	2 / 87 (2.30%)		
occurrences (all)	2		
Micturition urgency			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	1		
Proteinuria			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	1		
Hyperkalaemia			
subjects affected / exposed	1 / 87 (1.15%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 September 2019	In summary, the main changes included the following: • Further details on the pharmacokinetics of mangoral • Clarification to the text of the secondary objectives • Additional assessment of pregnancy testing for participant safety • Corrections made to the text describing variables and method for visualization of focal liver lesions • Clarification on the text for brain MRI procedures • Addition of an Independent Data Safety Monitoring Board • Clarification that the inter-reader agreement was to be evaluated by the intraclass correlation coefficient for the 2 co-primary efficacy variables based on the participant level.
23 April 2020	In summary, the main changes included the following: • Additional objectives included to ensure consistency with the variables analyzed • Revised some of the ranges of MRI parameters in Protocol Table 6 based on feedback received during the site initiation visits and discussions with the investigators • Clarification that the brain MRI is not a mandatory procedure • Additional exclusion criterion to exclude participants with simple liver cysts only • Revision of exclusion criterion 24 so as to allow patients with iron deficiency anemia or participants on iron therapy to enter the study as discussions with the investigators revealed that neither iron therapy nor iron deficiency anemia would jeopardize the analysis of the variables • Exclusion of participants with conditions that could interfere with excretion of mangoral • Revised details of prohibited concomitant medications specifically dietary iron supplementation • Additional detail to the primary objective to only include lesions identified on unenhanced images in analysis of co-primary efficacy variables • Addition of a fourth reader who was not included in the efficacy reads to track and match detected lesions on unenhanced MRI, mangoral-enhanced MRI, and combined MRI as per Food and Drug Administration recommendations • Clarification of analysis populations • Revision of the primary efficacy analysis to use mean scores instead of sum scores and to include an analysis of comparison between unenhanced MRI and mangoral-enhanced MRI alone in the same way as the primary analysis • Addition of both inter-reader and intra-reader agreement analysis.
06 July 2020	In summary, the main changes included the following: • Increase in the number of sites • Correction of IMP shelf life.
06 April 2021	In summary, the main changes included the following: • Clarification of inclusion criteria defining chronic kidney disease according to clinical practice and guidelines • Clarification of inclusion criteria to achieve approximately a 20% hepatic carcinoma cap • Clarification to the primary objective to align with exclusion criterion 1 (participants with simple liver lesions only) • Revision to MRI parameters to fit with sites' clinical practices and MRI machine settings • Clarification that new or worsening events should be reported as an adverse event (irrespective of clinical significance) if observed after IMP administration compared to previous predose assessments • Revision to assessment of serious adverse event to include seizure, stroke, cerebral venous thrombosis, and QTcF or QTcB >480 msec or QTcF or QTcB increase of 60 msec over baseline as important medical events.

12 October 2021	In summary, the main changes included the following: • Revision to the inclusion criteria so participants requiring dialysis are allowed at all sites • Added a section on permitted oral intake to include glucose or juice intake during the fasting period to treat hypoglycemia or diabetes mellitus type I and type II • Revision to exclusion criteria to remove the restriction of moderate hepatic impairment (Child-Pugh score B) • Removal of the exclusion criteria for patients on dialysis (excluding patients in the pharmacokinetic [PK] subgroup) • Changed follow up 1 (Visit 4) and follow up 2 (Visit 5) to optional remote visits (excluding patients from the PK subgroup).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported