Clinical trial results:
A Phase 2 Double-blind, Randomized, Placebo-controlled, Dose-finding Study to Evaluate the Safety, Tolerability and Efficacy of Volixibat Potassium, an Apical Sodium-Dependent Bile Acid Transporter Inhibitor (ASBTi) in Adults with Nonalcoholic Steatohepatitis (NASH)

Summary

EudraCT number	2016-000203-82
Trial protocol	GB
Global end of trial date	27 July 2018

Results information

Result version number	v1 (current)
This version publication date	24 February 2019
First version publication date	24 February 2019

Trial information

Trial identification

Sponsor protocol code	SHP626-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02787304
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire
Sponsor organisation address	300 Shire Way, Lexington, United States, MA 02421
Public contact	Study Director, Shire, ClinicalTransparency@shire.com
Scientific contact	Study Director, Shire, ClinicalTransparency@shire.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	27 July 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 July 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial was to evaluate the effect of volixibat compared to placebo (PBO) on liver histology.

Protection of trial subjects:

This study was conducted in accordance with current applicable regulations, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Europen Union (EU) Directive 2001/20/EC and its updates, and local ethical and legal requirements.

Background therapy:

None

Evidence for comparator:

N/A

Actual start date of recruitment	24 October 2016
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	Canada: 15
Country: Number of subjects enrolled	United Kingdom: 24
Country: Number of subjects enrolled	United States: 158
Worldwide total number of subjects	197
EEA total number of subjects	24

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)	152

From 65 to 84 years	45
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 68 centers in the United States of America, Canada, and the United Kingdom between 24 October 2016 (first subject first visit) and 27 July 2018 (last subject last visit).

Pre-assignment

Screening details:

A total of 585 subjects were screened to randomize 197 subjects, of which 196 subjects were analyzed for safety; 1 subject was randomized but was lost to follow-up after the baseline visit.

Period 1

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

Blinding implementation details:

The IP was supplied as double-blind blister packs. The actual double-blind treatment given to individual subjects was determined by a randomization schedule which was automatically assigned by the interactive response technology (IRT). Placebo capsules, which exactly matched the IP, were used in the blister packs to provide the same number and size capsules for each of the doses within the treatment groups.

Arms

Are arms mutually exclusive?	Yes
Arm title	SHP626 5 mg

Arm description:

Subjects received 5 milligrams (mg) of SHP626 (Volixibat potassium) capsule once daily (QD) by mouth (PO) for ≥24 weeks.

Arm type	Experimental
Investigational medicinal product name	Volixibat potassium
Investigational medicinal product code	SHP626
Other name	Volixibat
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received 5/10/20 mg of SHP626 capsule orally QD for ≥24 weeks.

Arm title	SHP626 10 mg

Arm description:

Subjects received 10 mg of SHP626 capsule QD PO for ≥24 weeks.

Arm type	Experimental
Investigational medicinal product name	Volixibat potassium
Investigational medicinal product code	SHP626
Other name	Volixibat
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received 5/10/20 mg of SHP626 capsule orally QD for ≥24 weeks.

Arm title	SHP626 20 mg

Arm description:

Subjects received 20 mg of SHP626 capsule QD PO for ≥24 weeks.

Arm type	Experimental
Investigational medicinal product name	Volixibat potassium
Investigational medicinal product code	SHP626
Other name	Volixibat
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received 5/10/20 mg of SHP626 capsule orally QD for ≥24 weeks.

Arm title	Placebo (PBO)

Arm description:

Subjects received placebo matched to SHP626 capsule QD PO for ≥24 weeks

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

Dosage and administration details:

Subjects received placebo matched to SHP626 capsule orally QD for ≥24 weeks.

Number of subjects in period 1[1]	SHP626 5 mg	SHP626 10 mg	SHP626 20 mg
Started	49	49	49
Completed	13	12	8
Not completed	36	37	41
Physician decision	-	-	1
Study terminated by sponsor	25	31	31
Adverse event	9	3	8
Non-compliance with study drug	-	-	1
Lost to follow-up	1	-	-
Withdrawal by subject	1	3	-

Number of subjects in period 1[1]	Placebo (PBO)
Started	49
Completed	15
Not completed	34
Physician decision	-
Study terminated by sponsor	32
Adverse event	1
Non-compliance with study drug	-
Lost to follow-up	1
Withdrawal by subject	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: All enrolled subjects were not treated with study drug. As baseline included only treated subjects, the worldwide number enrolled in the trial differs with the number of subjects reported in the baseline period.

Baseline characteristics

Reporting groups	
Reporting group title	SHP626 5 mg
Reporting group description:	
Subjects received 5 milligrams (mg) of SHP626 (Volixibat potassium) capsule once daily (QD) by mouth (PO) for ≥24 weeks.	
Reporting group title	SHP626 10 mg
Reporting group description:	
Subjects received 10 mg of SHP626 capsule QD PO for ≥24 weeks.	
Reporting group title	SHP626 20 mg
Reporting group description:	
Subjects received 20 mg of SHP626 capsule QD PO for ≥24 weeks.	
Reporting group title	Placebo (PBO)
Reporting group description:	
Subjects received placebo matched to SHP626 capsule QD PO for ≥24 weeks	

Reporting group values	SHP626 5 mg	SHP626 10 mg	SHP626 20 mg
Number of subjects	49	49	49
Age categorical Units: Subjects			
Age continuous			
Safety analysis set (SAS) consisted of all subjects who took at least 1 dose of randomized investigational product (IP), and had at least 1 postbaseline safety assessment.			
Units: years			
arithmetic mean	52.8	53.0	53.2
standard deviation	± 14.13	± 11.84	± 13.61
Gender categorical			
SAS consisted of all subjects who took at least 1 dose of randomized IP, and had at least 1 postbaseline safety assessment.			
Units:			
Male	22	15	24
Female	27	34	25

Reporting group values	Placebo (PBO)	Total	
Number of subjects	49	196	
Age categorical Units: Subjects			
Age continuous			
Safety analysis set (SAS) consisted of all subjects who took at least 1 dose of randomized investigational product (IP), and had at least 1 postbaseline safety assessment.			
Units: years			
arithmetic mean	53.4		
standard deviation	± 11.75	-	
Gender categorical			
SAS consisted of all subjects who took at least 1 dose of randomized IP, and had at least 1 postbaseline safety assessment.			
Units:			

Male	17	78	
Female	32	118	

End points

End points reporting groups

Reporting group title	SHP626 5 mg
Reporting group description:	
Subjects received 5 milligrams (mg) of SHP626 (Volixibat potassium) capsule once daily (QD) by mouth (PO) for ≥24 weeks.	
Reporting group title	SHP626 10 mg
Reporting group description:	
Subjects received 10 mg of SHP626 capsule QD PO for ≥24 weeks.	
Reporting group title	SHP626 20 mg
Reporting group description:	
Subjects received 20 mg of SHP626 capsule QD PO for ≥24 weeks.	
Reporting group title	Placebo (PBO)
Reporting group description:	
Subjects received placebo matched to SHP626 capsule QD PO for ≥24 weeks	

Primary: Number of Subjects Achieving Binary Response at Week 48

End point title	Number of Subjects Achieving Binary Response at Week 48[1]
End point description:	
Binary response indicating (yes/no) whether a subject responded at week 48 with a reduction of at least 2 points, without worsening of fibrosis, from baseline nonalcoholic fatty Liver disease (NAFLD) activity Score (NAS). The NAS grades NAFLD on liver biopsy based on the individual scoring of steatosis, inflammation and ballooning. The NAS is assessed on a scale of 0 to 8 with higher scores indicating more severe disease and lower scores indicating less severe disease. NAS is obtained by adding steatosis(assessed on a scale of 0 to 3), inflammation (assessed on a scale of 0 to 3) and ballooning (assessed on a scale of 0 to 2). Full analysis set (FAS) consisted of all subjects in the SAS who had at least 1 post-baseline efficacy assessment. Here number of subjects analyzed refer to subjects with liver biopsy at both Baseline and Week 48. Subjects who achieved the response "Yes" were reported.	
End point type	Primary
End point timeframe:	
Baseline, Week 48	
Notes:	
[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Descriptive statistics was done, No inferential statistics was performed.	

End point values	SHP626 5 mg	SHP626 10 mg	SHP626 20 mg	Placebo (PBO)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	11	8	13
Units: Subjects	4	2	3	5

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With a Change from Baseline to Week 48 in Liver Histology NAS Score

End point title	Number of Subjects With a Change from Baseline to Week 48 in Liver Histology NAS Score

End point description:

Change in liver histology was measured by the individual NAS components (ballooning, inflammation, steatosis). The NAS grades NAFLD on liver biopsy based on the individual scoring of steatosis, inflammation and ballooning. The NAS is assessed on a scale of 0 to 8 with higher scores indicating more severe disease and lower scores indicating less severe disease. NAS is obtained by adding steatosis (assessed on a scale of 0 to 3), inflammation (assessed on a scale of 0 to 3) and ballooning (assessed on a scale of 0 to 2). FAS consisted of all subjects in the SAS who had at least 1 postbaseline efficacy assessment. Here number of subjects analyzed refer to subjects with liver biopsy at both Baseline and Week 48.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	SHP626 5 mg	SHP626 10 mg	SHP626 20 mg	Placebo (PBO)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	11	8	13
Units: Subjects				
Increase in Score >=1	2	1	2	1
Stable in Score	2	3	2	1
Decrease in Score by 1	2	4	0	4
Decrease in Score >= 2	5	3	4	7

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 24 on Hepatic Steatosis as Measured by Magnetic Resonance Imaging-proton Density Fat-fraction (MRI-PDFF)

End point title	Change from Baseline to Week 24 on Hepatic Steatosis as Measured by Magnetic Resonance Imaging-proton Density Fat-fraction (MRI-PDFF)

End point description:

Hepatic steatosis was evaluated by measuring the reduction of liver fat with MRI-PDFF. Interim Analysis Set (IAS) consisted of all subjects in the SAS (subjects who had taken at least 1 dose of randomized IP, and had at least 1 post-baseline safety assessment) who have both baseline and scheduled Week 24 efficacy assessment (MRI and ALT biochemistry measurement) at the data cut time of the interim analysis (IA).

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	SHP626 5 mg	SHP626 10 mg	SHP626 20 mg	Placebo (PBO)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	20	18	21
Units: Percentage of liver fat				
arithmetic mean (standard deviation)	-0.35 (± 5.731)	-0.23 (± 7.914)	-1.29 (± 4.846)	0.15 (± 5.106)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With a Change from Baseline to Week 48 on Liver Histology as Measured by Fibrosis Stage (NASH)

End point title	Number of Subjects With a Change from Baseline to Week 48 on Liver Histology as Measured by Fibrosis Stage (NASH)

End point description:

Fibrosis stage was assessed on a scale of 0-4 with higher scores indicating more severe disease and lower scores indicating less severe disease (F0= no fibrosis, F4=cirrhosis). FAS consisted of all subjects in the SAS (subjects who had taken at least 1 dose of randomized IP, and had at least 1 postbaseline safety assessment) who had at least 1 postbaseline efficacy assessment. Here number of subjects analyzed refer to subjects with liver biopsy at both Baseline and Week 48.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	SHP626 5 mg	SHP626 10 mg	SHP626 20 mg	Placebo (PBO)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	11	8	13
Units: Subjects				
number (not applicable)				
Subjects with Increased score	2	4	4	4
Subjects with Stable score	4	5	3	4
Subjects with Decreased score	5	2	1	5

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Resolution of NASH at Week 48

End point title	Number of Subjects With Resolution of NASH at Week 48

End point description:

Resolution of NASH was defined as total absence of ballooning [score =0], absent or mild inflammation [score 0-1], steatosis can be present [score 0-3]) without worsening of fibrosis as assessed by liver histology.

End point type	Secondary

End point timeframe:
Week 48

End point values	SHP626 5 mg	SHP626 10 mg	SHP626 20 mg	Placebo (PBO)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	11	8	13
Units: Subjects	2	2	2	4

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 48 on Serum Liver-related Biochemistry

End point title	Change from Baseline to Week 48 on Serum Liver-related Biochemistry

End point description:

Serum liver-related biochemistry analysed by measuring alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT) was reported. SAS consisted of all subjects who took at least 1 dose of randomized IP, and had at least 1 postbaseline safety assessment. Here number of subjects analyzed refer to subjects evaluable for this outcome at specified timepoints.

End point type	Secondary

End point timeframe:
Baseline, Week 48

End point values	SHP626 5 mg	SHP626 10 mg	SHP626 20 mg	Placebo (PBO)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	49	49	49	49
Units: Units per liter (U/L)				
arithmetic mean (standard deviation)				
ALT (n=18,16,15,20)	1.2 (± 25.83)	4.2 (± 33.65)	-6.9 (± 37.91)	-0.2 (± 24.93)
AST (n=18,16,14,20)	7.6 (± 16.57)	10.6 (± 31.23)	-7.2 (± 27.08)	-0.8 (± 14.45)
ALP (n=18,16,15,20)	5.3 (± 9.62)	-0.9 (± 27.37)	-0.1 (± 14.82)	-0.7 (± 10.66)
GGT (n=18,16,15,20)	8.8 (± 46.24)	5.2 (± 47.24)	-8.8 (± 45.43)	-8.5 (± 41.11)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 48 on Serum Liver-related Biochemistry-Total Bilirubin (TB)

End point title	Change from Baseline to Week 48 on Serum Liver-related

	Biochemistry- Total Bilirubin (TB)

End point description:

Serum liver-related biochemistry analysed by measuring total bilirubin (TB) was reported. SAS consisted of all subjects who took at least 1 dose of randomized IP, and had at least 1 postbaseline safety assessment. Here number of subjects analyzed refer to subjects evaluable for this outcome at specified timepoints.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	SHP626 5 mg	SHP626 10 mg	SHP626 20 mg	Placebo (PBO)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	16	15	20
Units: Milligrams per deciliter (mg/dL)				
arithmetic mean (standard deviation)	0.019 (± 0.2198)	0.124 (± 0.2872)	0.060 (± 0.2730)	0.058 (± 0.1762)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 48 in Serum Glucose Level

End point title	Change from Baseline to Week 48 in Serum Glucose Level

End point description:

Change from baseline to Week 48 in serum glucose level was reported. SAS consisted of all subjects who took at least 1 dose of randomized IP, and had at least 1 postbaseline safety assessment. Here number of subjects analyzed refer to subjects evaluable for this outcome at specified timepoints.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	SHP626 5 mg	SHP626 10 mg	SHP626 20 mg	Placebo (PBO)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	16	15	20
Units: Milligrams per deciliter (mg/dL)				
arithmetic mean (standard deviation)	3.5 (± 40.07)	-5.0 (± 23.11)	1.6 (± 21.31)	15.6 (± 45.84)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 48 in Hemoglobin A1C (HbA1c)

End point title	Change from Baseline to Week 48 in Hemoglobin A1C (HbA1c)

End point description:

Change from baseline to Week 48 in HbA1c was reported. SAS consisted of all subjects who took at least 1 dose of randomized IP, and had at least 1 postbaseline safety assessment. Here number of subjects analyzed refer to subjects evaluable for this outcome at specified timepoints.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	SHP626 5 mg	SHP626 10 mg	SHP626 20 mg	Placebo (PBO)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	16	15	20
Units: Fraction of 1				
arithmetic mean (standard deviation)	-0.0003 (± 0.00559)	-0.0008 (± 0.00552)	-0.0020 (± 0.00426)	0.0033 (± 0.00701)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 48 in Serum Lipids

End point title	Change from Baseline to Week 48 in Serum Lipids

End point description:

Serum lipids level was measured by assessing cholesterol, high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), and triglycerides. SAS consisted of all subjects who took at least 1 dose of randomized IP, and had at least 1 postbaseline safety assessment. Here number of subjects analyzed refer to subjects evaluable for this outcome at specified timepoints.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	SHP626 5 mg	SHP626 10 mg	SHP626 20 mg	Placebo (PBO)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	16	15	20
Units: Milligrams per deciliter (mg/dL)				
arithmetic mean (standard deviation)				
Cholesterol	-13.4 (± 32.06)	-19.1 (± 38.26)	-7.6 (± 26.94)	4.7 (± 30.38)
HDL-C	1.8 (± 6.72)	2.2 (± 10.36)	2.7 (± 6.56)	0.0 (± 6.74)
LDL-C	-13.4 (± 27.38)	-19.5 (± 31.78)	-9.0 (± 22.37)	-0.8 (± 26.12)
Triglycerides	-9.5 (± 37.05)	-0.2 (± 92.34)	-7.2 (± 71.62)	28.7 (± 52.48)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From start of treatment up to follow-up (Week 52)	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0
Reporting groups	
Reporting group title	SHP626 5 Milligram (mg)
Reporting group description:	
Subject administered 5 mg SHP626 capsule by orally once daily in a double-blinded fashion	
Reporting group title	SHP626 10 Milligram (mg)
Reporting group description:	
Subject administered 10 mg SHP626 capsule by orally once daily in a double-blinded fashion	
Reporting group title	SHP626 20 Milligram (mg)
Reporting group description:	
Subject administered 20 mg SHP626 capsule by orally once daily in a double-blinded fashion	
Reporting group title	Placebo (PBO)
Reporting group description:	
Subject administered SHP626 matching PBO capsule by orally once daily in a double-blinded fashion	

Serious adverse events	SHP626 5 Milligram (mg)	SHP626 10 Milligram (mg)	SHP626 20 Milligram (mg)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 49 (2.04%)	2 / 49 (4.08%)	0 / 49 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pituitary tumour			
subjects affected / exposed	0 / 49 (0.00%)	0 / 49 (0.00%)	0 / 49 (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
Nervous system disorders			
Seizure			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	0 / 49 (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
Syncope			

subjects affected / exposed	0 / 49 (0.00%)	0 / 49 (0.00%)	0 / 49 (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			
Chest pain			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	0 / 49 (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
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 49 (0.00%)	0 / 49 (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
Urinary tract infection			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	0 / 49 (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

Serious adverse events	Placebo (PBO)		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 49 (2.04%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pituitary tumour			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Seizure			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			

subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	SHP626 5 Milligram (mg)	SHP626 10 Milligram (mg)	SHP626 20 Milligram (mg)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 49 (85.71%)	42 / 49 (85.71%)	40 / 49 (81.63%)
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	0 / 49 (0.00%)
occurrences (all)	0	1	0
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 49 (2.04%)	3 / 49 (6.12%)	0 / 49 (0.00%)
occurrences (all)	1	3	0
Vitamin d decreased			
subjects affected / exposed	1 / 49 (2.04%)	1 / 49 (2.04%)	3 / 49 (6.12%)
occurrences (all)	1	1	4
Injury, poisoning and procedural			

complications			
Ligament sprain			
subjects affected / exposed	0 / 49 (0.00%)	3 / 49 (6.12%)	0 / 49 (0.00%)
occurrences (all)	0	3	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 49 (4.08%)	0 / 49 (0.00%)	4 / 49 (8.16%)
occurrences (all)	2	0	5
Headache			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	4 / 49 (8.16%)
occurrences (all)	1	0	4
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 49 (6.12%)	3 / 49 (6.12%)	3 / 49 (6.12%)
occurrences (all)	4	3	3
Oedema peripheral			
subjects affected / exposed	1 / 49 (2.04%)	1 / 49 (2.04%)	1 / 49 (2.04%)
occurrences (all)	1	1	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 49 (2.04%)	3 / 49 (6.12%)	1 / 49 (2.04%)
occurrences (all)	1	3	1
Abdominal distension			
subjects affected / exposed	3 / 49 (6.12%)	1 / 49 (2.04%)	0 / 49 (0.00%)
occurrences (all)	3	1	0
Abdominal pain			
subjects affected / exposed	10 / 49 (20.41%)	9 / 49 (18.37%)	6 / 49 (12.24%)
occurrences (all)	11	10	6
Abdominal pain upper			
subjects affected / exposed	0 / 49 (0.00%)	3 / 49 (6.12%)	3 / 49 (6.12%)
occurrences (all)	0	3	4
Constipation			
subjects affected / exposed	2 / 49 (4.08%)	4 / 49 (8.16%)	1 / 49 (2.04%)
occurrences (all)	2	4	1
Diarrhoea			

subjects affected / exposed	38 / 49 (77.55%)	35 / 49 (71.43%)	35 / 49 (71.43%)
occurrences (all)	43	46	47
Frequent bowel movements			
subjects affected / exposed	4 / 49 (8.16%)	1 / 49 (2.04%)	0 / 49 (0.00%)
occurrences (all)	4	1	0
Nausea			
subjects affected / exposed	5 / 49 (10.20%)	4 / 49 (8.16%)	7 / 49 (14.29%)
occurrences (all)	6	6	7
Vomiting			
subjects affected / exposed	1 / 49 (2.04%)	3 / 49 (6.12%)	4 / 49 (8.16%)
occurrences (all)	1	4	4
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 49 (6.12%)	2 / 49 (4.08%)	1 / 49 (2.04%)
occurrences (all)	3	3	1
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	3 / 49 (6.12%)	0 / 49 (0.00%)	0 / 49 (0.00%)
occurrences (all)	3	0	0
Hyperhidrosis			
subjects affected / exposed	3 / 49 (6.12%)	0 / 49 (0.00%)	0 / 49 (0.00%)
occurrences (all)	3	0	0
Pruritus			
subjects affected / exposed	0 / 49 (0.00%)	3 / 49 (6.12%)	1 / 49 (2.04%)
occurrences (all)	0	3	1
Rash			
subjects affected / exposed	0 / 49 (0.00%)	4 / 49 (8.16%)	1 / 49 (2.04%)
occurrences (all)	0	4	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 49 (0.00%)	2 / 49 (4.08%)	3 / 49 (6.12%)
occurrences (all)	0	2	3
Back pain			
subjects affected / exposed	0 / 49 (0.00%)	0 / 49 (0.00%)	3 / 49 (6.12%)
occurrences (all)	0	0	3
Infections and infestations			

Influenza			
subjects affected / exposed	3 / 49 (6.12%)	2 / 49 (4.08%)	0 / 49 (0.00%)
occurrences (all)	3	2	0
Nasopharyngitis			
subjects affected / exposed	1 / 49 (2.04%)	1 / 49 (2.04%)	3 / 49 (6.12%)
occurrences (all)	1	1	3
Sinusitis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	3 / 49 (6.12%)
occurrences (all)	1	0	3
Upper respiratory tract infection			
subjects affected / exposed	1 / 49 (2.04%)	4 / 49 (8.16%)	1 / 49 (2.04%)
occurrences (all)	1	4	1
Urinary tract infection			
subjects affected / exposed	1 / 49 (2.04%)	6 / 49 (12.24%)	1 / 49 (2.04%)
occurrences (all)	2	7	1

Non-serious adverse events	Placebo (PBO)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 49 (48.98%)		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	3		
Blood creatine phosphokinase increased			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	4		
Vitamin d decreased			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dizziness			

subjects affected / exposed	0 / 49 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	3		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences (all)	2		
Oedema peripheral			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	3		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences (all)	1		
Abdominal distension			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences (all)	2		
Abdominal pain			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	3		
Abdominal pain upper			
subjects affected / exposed	0 / 49 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	10 / 49 (20.41%)		
occurrences (all)	11		
Frequent bowel movements			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences (all)	1		
Nausea			

subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	2 / 49 (4.08%) 2 3 / 49 (6.12%) 3		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	 3 / 49 (6.12%) 4		
Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all) Hyperhidrosis subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 1 / 49 (2.04%) 1 0 / 49 (0.00%) 0 1 / 49 (2.04%) 1 2 / 49 (4.08%) 3		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all)	 0 / 49 (0.00%) 0 3 / 49 (6.12%) 3		
Infections and infestations Influenza subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	 1 / 49 (2.04%) 2 2 / 49 (4.08%) 5		

Sinusitis subjects affected / exposed occurrences (all)	1 / 49 (2.04%) 1		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 49 (4.08%) 2		
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 49 (2.04%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 April 2016	Amendment 1 • Requirement for meal fat content of 10-20 grams before daily dose of investigational product added • Planned duration of screening period increased from 42 to 56 days • Acceptable methods of contraception were modified to delete the use of double-barrier methods and clarify barrier methods, add male sterilization, add and define abstinence • Clarified that the Week 24 and Week 48 MRIs will be conducted for subjects in the IA set only
19 July 2016	Amendment 2 • Alcohol Test revised from Serum to Blood, Vitamins A and E were • Added to the schedule of assessments, MRI time points were clarified, and window for Visit 10 was added. • Exclusion criterion #24 regarding pregnant women, women who plan to become pregnant, or men who plan to father a child during the study, was added. • The list of acceptable methods of contraception was revised. • Clarified that abnormal screening labs may be repeated before determining screen failure.
22 March 2017	Amendment 3 • Extended planned study period from July 2019 to July 2020. • Revised 1) Eligibility criteria; 2) sample size description; and 3) definition of secondary endpoint • "Resolution of NASH" • Added mention that the number of F0 subjects will be capped at 81 if 1 dose is dropped after the interim analysis and at 62 if 2 doses are dropped. • Criterion #6 was revised to allow for F0 (fibrosis score), in addition to F1-F3. • Revised criteria #11 and #12 to allow for enrollment of subjects with elevation in AST (#11) and ALT (#12) up to 7 times the ULN (instead of 5 times the ULN). • Revised criterion #30 to remove exclusion of subjects who previously failed screening. • Increased approximate number of subjects screened from 334 to 677 subjects. • The definition of "Resolution of NASH" was revised.
25 August 2017	Amendment 4 • Reduced planned study period from July 2020 to January 2020. • The "Methodology" section was updated to reflect new numbers following elimination of the previously planned enrollment pause. • Lengthened screening window from 8 weeks (56 days) to 10 weeks (70 days). • Revised the capping number for F0 subjects; this will be capped at 88 if 1 dose is dropped after the interim analysis and at 78 if 2 doses are dropped (% remains the same at 30%) following elimination of the previously planned enrollment pause.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Based on predefined IA criteria at Week 24, an external independent DMC & an internal unblinded recommendation review team recommended study termination as no dose of Volixibat was effective, based on reduction of steatosis on MRIPDFF & ALT reduction

Notes: