



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), European 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 |
|-----------------|--------------------------------------------------------|

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 (\pm 0.00559) | -0.0008 (\pm 0.00552) | -0.0020 (\pm 0.00426) | 0.0033 (\pm 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 (\pm 32.06) | -19.1 (\pm 38.26) | -7.6 (\pm 26.94) | 4.7 (\pm 30.38) |
| HDL-C | 1.8 (\pm 6.72) | 2.2 (\pm 10.36) | 2.7 (\pm 6.56) | 0.0 (\pm 6.74) |
| LDL-C | -13.4 (\pm 27.38) | -19.5 (\pm 31.78) | -9.0 (\pm 22.37) | -0.8 (\pm 26.12) |
| Triglycerides | -9.5 (\pm 37.05) | -0.2 (\pm 92.34) | -7.2 (\pm 71.62) | 28.7 (\pm 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 occurrences (all) | 0 / 49 (0.00%) 0 | 3 / 49 (6.12%) 3 | 0 / 49 (0.00%) 0 |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) | 2 / 49 (4.08%) 2 1 / 49 (2.04%) 1 | 0 / 49 (0.00%) 0 0 / 49 (0.00%) 0 | 4 / 49 (8.16%) 5 4 / 49 (8.16%) 4 |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) | 3 / 49 (6.12%) 4 1 / 49 (2.04%) 1 | 3 / 49 (6.12%) 3 1 / 49 (2.04%) 1 | 3 / 49 (6.12%) 3 1 / 49 (2.04%) 1 |
| Gastrointestinal disorders Abdominal discomfort subjects affected / exposed occurrences (all) Abdominal distension subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea | 1 / 49 (2.04%) 1 3 / 49 (6.12%) 3 10 / 49 (20.41%) 11 0 / 49 (0.00%) 0 2 / 49 (4.08%) 2 | 3 / 49 (6.12%) 3 1 / 49 (2.04%) 1 9 / 49 (18.37%) 10 3 / 49 (6.12%) 3 4 / 49 (8.16%) 4 | 1 / 49 (2.04%) 1 0 / 49 (0.00%) 0 6 / 49 (12.24%) 6 3 / 49 (6.12%) 4 1 / 49 (2.04%) 1 |

| | | | |
|-------------------------------------------------------------------------------------------------------------------|------------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 38 / 49 (77.55%) 43 | 35 / 49 (71.43%) 46 | 35 / 49 (71.43%) 47 |
| Frequent bowel movements subjects affected / exposed occurrences (all) | 4 / 49 (8.16%) 4 | 1 / 49 (2.04%) 1 | 0 / 49 (0.00%) 0 |
| Nausea subjects affected / exposed occurrences (all) | 5 / 49 (10.20%) 6 | 4 / 49 (8.16%) 6 | 7 / 49 (14.29%) 7 |
| Vomiting subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 | 3 / 49 (6.12%) 4 | 4 / 49 (8.16%) 4 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 3 / 49 (6.12%) 3 | 2 / 49 (4.08%) 3 | 1 / 49 (2.04%) 1 |
| Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all) | 3 / 49 (6.12%) 3 | 0 / 49 (0.00%) 0 | 0 / 49 (0.00%) 0 |
| Hyperhidrosis subjects affected / exposed occurrences (all) | 3 / 49 (6.12%) 3 | 0 / 49 (0.00%) 0 | 0 / 49 (0.00%) 0 |
| Pruritus subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 3 / 49 (6.12%) 3 | 1 / 49 (2.04%) 1 |
| Rash subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 4 / 49 (8.16%) 4 | 1 / 49 (2.04%) 1 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 2 / 49 (4.08%) 2 | 3 / 49 (6.12%) 3 |
| Back pain subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 0 / 49 (0.00%) 0 | 3 / 49 (6.12%) 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 occurrences (all) | 0 / 49 (0.00%) 0 | | |
| Headache subjects affected / exposed occurrences (all) | 3 / 49 (6.12%) 3 | | |
| General disorders and administration site conditions | | | |
| Fatigue subjects affected / exposed occurrences (all) | 2 / 49 (4.08%) 2 | | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 3 / 49 (6.12%) 3 | | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 | | |
| Abdominal distension subjects affected / exposed occurrences (all) | 2 / 49 (4.08%) 2 | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 3 / 49 (6.12%) 3 | | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | | |
| Constipation subjects affected / exposed occurrences (all) | 3 / 49 (6.12%) 3 | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 10 / 49 (20.41%) 11 | | |
| Frequent bowel movements subjects affected / exposed occurrences (all) | 1 / 49 (2.04%) 1 | | |
| Nausea | | | |

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 08 April 2016 | Amendment 1 <ul style="list-style-type: none">Requirement for meal fat content of 10-20 grams before daily dose of investigational product addedPlanned duration of screening period increased from 42 to 56 daysAcceptable methods of contraception were modified to delete the use of double-barrier methods and clarify barrier methods, add male sterilization, add and define abstinenceClarified that the Week 24 and Week 48 MRIs will be conducted for subjects in the IA set only |
| 19 July 2016 | Amendment 2 <ul style="list-style-type: none">Alcohol Test revised from Serum to Blood, Vitamins A and E wereAdded 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 <ul style="list-style-type: none">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 <ul style="list-style-type: none">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: