Clinical trial results:
A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, and Efficacy of GS-9674 in Subjects with Nonalcoholic Steatohepatitis (NASH).

Summary

EudraCT number	2016-002496-10
Trial protocol	AT GB
Global end of trial date	09 January 2018

Results information

Result version number	v2 (current)
This version publication date	18 May 2019
First version publication date	23 January 2019
Version creation reason	• Correction of full data set Adding text to "Limitations and Caveats" section

Trial information

Trial identification

Sponsor protocol code	GS-US-402-1852

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02854605
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, CA, United States, 94404
Public contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com
Scientific contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.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	09 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 January 2018
Global end of trial reached?	Yes
Global end of trial date	09 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the safety and tolerability of GS-9674 in participants with nonalcoholic steatohepatitis (NASH).

Protection of trial subjects:

The protocol and consent/assent forms were submitted by each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent/assent forms (if applicable) after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements. This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 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: 25
Country: Number of subjects enrolled	Hong Kong: 10
Country: Number of subjects enrolled	New Zealand: 4
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	United States: 96
Worldwide total number of subjects	140
EEA total number of subjects	1

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)	121
From 65 to 84 years	19
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in North America, Hong Kong, New Zealand, and Europe. The first participant was screened on 26 October 2016. The last study visit occurred on 09 January 2018.

Pre-assignment

Screening details:

327 participants were screened.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	GS-9674 100 mg

Arm description:

GS-9674 100 mg tablet once daily + placebo-to-match (PTM) GS-9674 30 mg tablet once daily for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	GS-9674
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

100 mg administered once daily

Investigational medicinal product name	PTM GS-9674 30 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered once daily

Arm title	GS-9674 30 mg

Arm description:

GS-9674 30 mg tablet once daily + PTM GS-9674 100 mg tablet once daily for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	GS-9674
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

30 mg administered once daily

Investigational medicinal product name	PTM GS-9674 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
Administered once daily

Arm title	Placebo

Arm description:
PTM GS-9674 30 mg tablet once daily + PTM GS-9674 100 mg tablet once daily for 24 weeks.

Arm type	Placebo
Investigational medicinal product name	PTM GS-9674 30 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
Administered once daily

Investigational medicinal product name	PTM GS-9674 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
Administered once daily

Number of subjects in period 1	GS-9674 100 mg	GS-9674 30 mg	Placebo
Started	56	56	28
Completed	53	49	24
Not completed	3	7	4
Protocol violation	-	-	1
Adverse event	1	5	2
Withdrew consent	1	-	1
Investigator's discretion	1	-	-
Lost to follow-up	-	2	-

Baseline characteristics

Reporting groups	
Reporting group title	GS-9674 100 mg
Reporting group description:	
GS-9674 100 mg tablet once daily + placebo-to-match (PTM) GS-9674 30 mg tablet once daily for 24 weeks.	
Reporting group title	GS-9674 30 mg
Reporting group description:	
GS-9674 30 mg tablet once daily + PTM GS-9674 100 mg tablet once daily for 24 weeks.	
Reporting group title	Placebo
Reporting group description:	
PTM GS-9674 30 mg tablet once daily + PTM GS-9674 100 mg tablet once daily for 24 weeks.	

Reporting group values	GS-9674 100 mg	GS-9674 30 mg	Placebo
Number of subjects	56	56	28
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	55	51	50
standard deviation	± 10.5	± 12.8	± 9.9
Gender categorical			
Units: Subjects			
Female	35	37	15
Male	21	19	13
Ethnicity			
Units: Subjects			
Hispanic or Latino	17	19	8
Not Hispanic or Latino	39	37	20
Race			
Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	13	5	4
Native Hawaiian or Other Pacific Islander	0	2	0
Black or African American	1	1	1
White	42	47	21
Other	0	0	1

Reporting group values	Total		
Number of subjects	140		
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean			

standard deviation	-		

Gender categorical Units: Subjects			
Female	87		
Male	53		
Ethnicity Units: Subjects			
Hispanic or Latino	44		
Not Hispanic or Latino	96		
Race Units: Subjects			
American Indian or Alaska Native	2		
Asian	22		
Native Hawaiian or Other Pacific Islander	2		
Black or African American	3		
White	110		
Other	1		

End points

End points reporting groups

Reporting group title	GS-9674 100 mg
Reporting group description:	
GS-9674 100 mg tablet once daily + placebo-to-match (PTM) GS-9674 30 mg tablet once daily for 24 weeks.	
Reporting group title	GS-9674 30 mg
Reporting group description:	
GS-9674 30 mg tablet once daily + PTM GS-9674 100 mg tablet once daily for 24 weeks.	
Reporting group title	Placebo
Reporting group description:	
PTM GS-9674 30 mg tablet once daily + PTM GS-9674 100 mg tablet once daily for 24 weeks.	

Primary: Overall Safety of GS-9674 as Assessed By Percentage of Participants Experiencing Treatment-Emergent Adverse Events (TEAEs)

End point title	Overall Safety of GS-9674 as Assessed By Percentage of Participants Experiencing Treatment-Emergent Adverse Events (TEAEs)[1]
End point description:	
TEAEs were defined as 1 or both of the following: 1) Any AEs with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug, 2) Any AEs leading to premature discontinuation of study drug. Safety Analysis Set included all participants who took at least 1 dose of study drug.	
End point type	Primary
End point timeframe:	
Up to 24 weeks plus 30 days	

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: No statistical analyses was planned for this endpoint.

End point values	GS-9674 100 mg	GS-9674 30 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56	56	28	
Units: Percentage of participants				
number (not applicable)				
TEAEs	89.3	76.8	67.9	
TEAEs leading to premature discontinuation of drug	1.8	8.9	7.1	

Statistical analyses

No statistical analyses for this end point

Primary: Overall Safety of GS-9674 as Assessed By Percentage of Participants With Treatment-Emergent Laboratory Abnormalities

End point title	Overall Safety of GS-9674 as Assessed By Percentage of

	Participants With Treatment-Emergent Laboratory Abnormalities[2]

End point description:

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any post-baseline time point, up to and including the date of last dose of study drug plus 30 days for participants who permanently discontinued study. Participants in the Safety Analysis Set were analyzed.

End point type	Primary

End point timeframe:

Up to 24 weeks plus 30 days

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses was planned for this endpoint.

End point values	GS-9674 100 mg	GS-9674 30 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56	56	28	
Units: Percentage of participants				
number (not applicable)				
Any Grade ≥ 1	89.3	92.9	92.9	
Grade 1	35.7	42.9	50.0	
Grade 2	37.5	37.5	25.0	
Grade 3	7.1	10.7	14.3	
Grade 4	8.9	1.8	3.6	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 24 weeks plus 30 days	
Adverse event reporting additional description:	
Safety Analysis Set included all participants who took at least 1 dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups	
Reporting group title	GS-9674 30 mg
Reporting group description:	
GS-9674 30 mg tablet once daily + PTM GS-9674 100 mg tablet once daily for 24 weeks.	
Reporting group title	Placebo
Reporting group description:	
PTM GS-9674 30 mg tablet once daily + PTM GS-9674 100 mg tablet once daily for 24 weeks.	
Reporting group title	GS-9674 100 mg
Reporting group description:	
GS-9674 100 mg tablet once daily + PTM GS-9674 30 mg tablet once daily for 24 weeks.	

Serious adverse events	GS-9674 30 mg	Placebo	GS-9674 100 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 56 (3.57%)	1 / 28 (3.57%)	2 / 56 (3.57%)
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)			
B-cell lymphoma			
subjects affected / exposed	1 / 56 (1.79%)	0 / 28 (0.00%)	0 / 56 (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
Oesophageal carcinoma			
subjects affected / exposed	0 / 56 (0.00%)	0 / 28 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid cancer			

subjects affected / exposed	1 / 56 (1.79%)	0 / 28 (0.00%)	0 / 56 (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
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 56 (0.00%)	1 / 28 (3.57%)	0 / 56 (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
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 56 (1.79%)	0 / 28 (0.00%)	0 / 56 (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
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 56 (0.00%)	0 / 28 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	GS-9674 30 mg	Placebo	GS-9674 100 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 56 (60.71%)	17 / 28 (60.71%)	39 / 56 (69.64%)
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 56 (0.00%)	2 / 28 (7.14%)	0 / 56 (0.00%)
occurrences (all)	0	2	0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 56 (1.79%)	0 / 28 (0.00%)	3 / 56 (5.36%)
occurrences (all)	1	0	3
Nervous system disorders			
Headache			

subjects affected / exposed	6 / 56 (10.71%)	4 / 28 (14.29%)	4 / 56 (7.14%)
occurrences (all)	9	4	5
Dizziness			
subjects affected / exposed	1 / 56 (1.79%)	2 / 28 (7.14%)	1 / 56 (1.79%)
occurrences (all)	1	2	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	7 / 56 (12.50%)	1 / 28 (3.57%)	2 / 56 (3.57%)
occurrences (all)	7	1	2
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 56 (0.00%)	0 / 28 (0.00%)	3 / 56 (5.36%)
occurrences (all)	0	0	3
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	5 / 56 (8.93%)	1 / 28 (3.57%)	3 / 56 (5.36%)
occurrences (all)	6	1	3
Abdominal distension			
subjects affected / exposed	3 / 56 (5.36%)	3 / 28 (10.71%)	2 / 56 (3.57%)
occurrences (all)	3	3	2
Nausea			
subjects affected / exposed	4 / 56 (7.14%)	2 / 28 (7.14%)	2 / 56 (3.57%)
occurrences (all)	6	2	2
Abdominal pain			
subjects affected / exposed	2 / 56 (3.57%)	0 / 28 (0.00%)	5 / 56 (8.93%)
occurrences (all)	2	0	5
Diarrhoea			
subjects affected / exposed	3 / 56 (5.36%)	1 / 28 (3.57%)	3 / 56 (5.36%)
occurrences (all)	3	1	4
Constipation			
subjects affected / exposed	3 / 56 (5.36%)	0 / 28 (0.00%)	1 / 56 (1.79%)
occurrences (all)	3	0	1
Dry mouth			
subjects affected / exposed	1 / 56 (1.79%)	2 / 28 (7.14%)	1 / 56 (1.79%)
occurrences (all)	1	2	1
Dyspepsia			

subjects affected / exposed	0 / 56 (0.00%)	2 / 28 (7.14%)	1 / 56 (1.79%)
occurrences (all)	0	2	1
Gastritis			
subjects affected / exposed	0 / 56 (0.00%)	2 / 28 (7.14%)	0 / 56 (0.00%)
occurrences (all)	0	2	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	9 / 56 (16.07%)	5 / 28 (17.86%)	13 / 56 (23.21%)
occurrences (all)	9	6	15
Pruritus generalised			
subjects affected / exposed	3 / 56 (5.36%)	0 / 28 (0.00%)	3 / 56 (5.36%)
occurrences (all)	3	0	3
Psychiatric disorders			
Depression			
subjects affected / exposed	5 / 56 (8.93%)	0 / 28 (0.00%)	1 / 56 (1.79%)
occurrences (all)	5	0	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 56 (7.14%)	3 / 28 (10.71%)	2 / 56 (3.57%)
occurrences (all)	4	3	2
Myalgia			
subjects affected / exposed	1 / 56 (1.79%)	1 / 28 (3.57%)	3 / 56 (5.36%)
occurrences (all)	1	1	3
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	5 / 56 (8.93%)	2 / 28 (7.14%)	6 / 56 (10.71%)
occurrences (all)	5	3	7
Nasopharyngitis			
subjects affected / exposed	3 / 56 (5.36%)	3 / 28 (10.71%)	1 / 56 (1.79%)
occurrences (all)	4	5	1
Bronchitis			
subjects affected / exposed	3 / 56 (5.36%)	0 / 28 (0.00%)	3 / 56 (5.36%)
occurrences (all)	3	0	3
Urinary tract infection			
subjects affected / exposed	0 / 56 (0.00%)	1 / 28 (3.57%)	4 / 56 (7.14%)
occurrences (all)	0	1	4

Sinusitis subjects affected / exposed occurrences (all)	3 / 56 (5.36%) 3	0 / 28 (0.00%) 0	1 / 56 (1.79%) 1
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	0 / 56 (0.00%) 0	2 / 28 (7.14%) 2	0 / 56 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 October 2016	- Updated inclusion criteria to allow for histological evidence of fatty liver within 2 years of - screening and to ensure subjects with cirrhosis or liver disease were not enrolled in the study - Added exclusion criterion (HbA1c > 9% at screening) to ensure subjects with poorly - controlled diabetes were not enrolled in the study - Provided additional nonclinical safety data - Updated data from other clinical studies of GS-9674 - Updated the risk/benefit assessment to communicate the risk for liver injury and provide newly available safety data - Added guidance regarding concomitant use of atorvastatin - Updated the list of prohibited medications based on newly available drug-drug interaction data - Allowed subjects to rescreen once for the study - Revised drug-induced liver injury (DILI) monitoring language to update thresholds, add creatine phosphokinase testing as a requirement for DILI observation, and to clarify study drug stopping rules - Allowed hormonal contraception as a highly effective contraceptive method
24 January 2017	-Allowed for a historical liver biopsy consistent with NASH and no documented weight loss > 5% between the date of the liver biopsy and screening to determine eligibility for enrollment - Extended screening period to up to 6 weeks - Lowered screening MRI-PDFF cutoff from ≥ 10% to ≥ 8% for detection of steatosis, and lowered screening MRE cutoff from ≥ 2.90 to ≥ 2.5 kPa for detection of hepatic fibrosis - Removed creatinine clearance inclusion criterion and replaced with criterion specifying a normal serum creatinine level - Added language to clarify that subjects with FibroSURE/FibroTest ≥ 0.75 were eligible for enrollment if a liver biopsy within 12 months of screening excluded cirrhosis. Additionally, direct bilirubin was used instead of total bilirubin in FibroSURE/FibroTest calculations for subjects with Gilbert's syndrome or hemolysis - Added nonclinical toxicology data to support dosing of subjects beyond 12 weeks - Clarified that study drug should not be administered within 4 hours of dosing with bile acid sequestrants - Provided guidance regarding retesting of exclusionary laboratory analyses during screening and allowed retesting to be performed at the principal investigator's discretion - Clarified that subjects who failed screening but met the revised inclusion/exclusion criteria were eligible for enrollment

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.

An unplanned review of unblinded clinical trial data was performed in this study that was not prospectively specified in the protocol. There was no impact on the overall integrity or conclusions of the study.

Notes: