Clinical trial results:
A Phase 2, Double-Blind, Randomized Study Evaluating the Safety, Tolerability, and Efficacy of GS-4997 in Combination with Prednisolone versus Prednisolone Alone in Subjects with Severe Alcoholic Hepatitis (AH)

Summary

EudraCT number	2016-000821-37
Trial protocol	AT BE GB
Global end of trial date	31 May 2018

Results information

Result version number	v1
This version publication date	06 January 2019
First version publication date	06 January 2019

Trial information

Trial identification

Sponsor protocol code	GS-US-416-2124

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02854631
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 Sciences, Gilead Clinical Study Information Center, GileadClinicalTrials@gilead.com
Scientific contact	Gilead Sciences, Gilead Clinical Study Information Center, 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	31 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 February 2018
Global end of trial reached?	Yes
Global end of trial date	31 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the safety and tolerability of selonsertib (GS-4997) in combination with prednisolone versus prednisolone alone in participants with severe alcoholic hepatitis (AH).

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	01 September 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	United States: 33
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	United Kingdom: 28
Worldwide total number of subjects	104
EEA total number of subjects	66

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	100
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in Europe and North America. The first participant was screened on 01 September 2016. The last study visit occurred on 31 May 2018. Two participants were randomized in the Selonsertib + Prednisolone arm but were never treated.

Pre-assignment

Screening details:

166 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	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Selonsertib + Prednisolone

Arm description:

Participants received selonsertib + prednisolone for 28 days.

Arm type	Experimental
Investigational medicinal product name	Selonsertib
Investigational medicinal product code	
Other name	GS-4997
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

18 mg administered for 28 days, without regard to food.

Investigational medicinal product name	Prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

40 mg (4 X 10 mg tablets) administered once daily for 28 days, without regard to food.

Arm title	Placebo + Prednisolone

Arm description:

Participants received placebo-to-match selonsertib + prednisolone for 28 days.

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

Dosage and administration details:

40 mg (4 X 10 mg tablets) administered orally once daily for 28 days, without regard to food.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo-to-match selonsertib tablets administered once daily for 28 days, without regard to food.

Number of subjects in period 1[1]	Selonsertib + Prednisolone	Placebo + Prednisolone
Started	50	52
Completed	26	37
Not completed	24	15
Adverse event, non-fatal	1	2
Protocol violation	-	1
Death	12	8
Liver biopsy inconsistent with diagnosis	2	-
Withdrew consent	3	2
Investigator's discretion	2	-
Lost to follow-up	4	2

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: Two participants were randomized in Selonsertib + Prednisolone arm but were never treated.

Baseline characteristics

Reporting groups	
Reporting group title	Selonsertib + Prednisolone
Reporting group description:	
Participants received selonsertib + prednisolone for 28 days.	

Reporting group title	Placebo + Prednisolone
Reporting group description:	
Participants received placebo-to-match selonsertib + prednisolone for 28 days.	

Reporting group values	Selonsertib + Prednisolone	Placebo + Prednisolone	Total
Number of subjects	50	52	102
Age categorical Units: Subjects			
Age continuous Units: years			
median	49	49	
standard deviation	± 10.0	± 9.3	-
Gender categorical Units: Subjects			
Female	21	16	37
Male	29	36	65
Ethnicity Units: Subjects			
Hispanic or Latino	1	1	2
Not Hispanic or Latino	46	49	95
Unknown or Not Reported	3	2	5
Race Units: Subjects			
Asian	2	4	6
Black or African American	0	2	2
White	44	44	88
Unknown or Not Reported	4	2	6
Hospitalized at Time of Screening Units: Subjects			
Yes	46	48	94
No	4	4	8
Baseline Infection Units: Subjects			
Yes	6	11	17
No	44	41	85
Days Hospitalized Prior to First Dose Date			
Only participants who were hospitalized were analyzed (Selonsertib + Prednisolone = 46; Placebo + Prednisolone = 48).			
Units: Days			
arithmetic mean	10	10	

standard deviation	± 4.6	± 5.2	-
Alanine Aminotransferase (ALT)			
# of Participants Analyzed: Selonsertib + Prednisolone = 49; Placebo + Prednisolone = 52			
Units: Units per liter (U/L)			
arithmetic mean	45	48	
standard deviation	± 33.5	± 23.2	-
Aspartate Aminotransferase (AST)			
# of Participants Analyzed: Selonsertib + Prednisolone = 49; Placebo + Prednisolone = 52			
Units: U/L			
arithmetic mean	122	129	
standard deviation	± 60.9	± 59.9	-
Gamma Glutamyl Transferase (GGT)			
# of Participants Analyzed: Selonsertib + Prednisolone = 30; Placebo + Prednisolone = 33			
Units: U/L			
arithmetic mean	238	278	
standard deviation	± 175.5	± 358.7	-
Alkaline Phosphatase			
# of Participants Analyzed: Selonsertib + Prednisolone = 49; Placebo + Prednisolone = 52			
Units: U/L			
arithmetic mean	162	189	
standard deviation	± 62.2	± 111.3	-
Bilirubin			
# of Participants Analyzed: Selonsertib + Prednisolone = 49; Placebo + Prednisolone = 52			
Units: Milligrams per deciliter (mg/dL)			
arithmetic mean	14.3	14.5	
standard deviation	± 8.35	± 7.78	-
Albumin			
# of Participants Analyzed: Selonsertib + Prednisolone = 49; Placebo + Prednisolone = 52			
Units: Grams per deciltre (g/dL)			
arithmetic mean	3.1	3.0	
standard deviation	± 0.62	± 0.53	-
International Normalized Ratio (INR)			
# of Participants Analyzed: Selonsertib + Prednisolone = 47; Placebo + Prednisolone = 52			
Units: Ratio			
arithmetic mean	1.7	1.6	
standard deviation	± 0.31	± 0.22	-
Model for End- Stage Liver Disease (MELD) Score			
Units: Units on a scale			
arithmetic mean	22	22	
standard deviation	± 4.2	± 4.4	-
Child-Pugh-Turcotte (CPT) Score			
# of Participants Analyzed: Selonsertib + Prednisolone = 47; Placebo + Prednisolone = 52			
Units: Units on a scale			
arithmetic mean	10	10	
standard deviation	± 1.2	± 1.3	-
Maddrey DF Score			
# of Participants Analyzed: Selonsertib + Prednisolone = 44; Placebo + Prednisolone = 52			
Units: Units on a scale			
arithmetic mean	42	38	
standard deviation	± 16.9	± 11.4	-

End points

End points reporting groups

Reporting group title	Selonsertib + Prednisolone
Reporting group description:	
Participants received selonsertib + prednisolone for 28 days.	

Reporting group title	Placebo + Prednisolone
Reporting group description:	
Participants received placebo-to-match selonsertib + prednisolone for 28 days.	

Primary: Percentage of Participants with Treatment-Emergent Adverse Events (AE), Serious AEs, AEs Leading to Premature Study Drug Discontinuation, and Grade 3 or 4 Laboratory Abnormalities

End point title	Percentage of Participants with Treatment-Emergent Adverse Events (AE), Serious AEs, AEs Leading to Premature Study Drug Discontinuation, and Grade 3 or 4 Laboratory Abnormalities[1]

End point description:

An AE was defined as any untoward medical occurrence that occurred during the course of the trial after study treatment had started. An adverse event was therefore any unfavorable and unintended sign, symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug. An SAE is any untoward medical occurrence that at any dose results in death, are life threatening, requires hospitalization or prolongation of hospitalization or results in disability/incapacity, and congenital anomaly/birth defect. Safety Analysis Set included participants who were randomized and took at least 1 dose of study drug.

End point type	Primary

End point timeframe:

Up to Day 28 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 the safety outcome.

End point values	Selonsertib + Prednisolone	Placebo + Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	52		
Units: Percentage of participants				
number (not applicable)				
TEAEs	94.0	94.2		
TE SAEs	50.0	40.4		
TEAEs (discontinuation of Selonsertib/Placebo)	18.0	7.7		
TEAEs (discontinuation of Prednisolone)	14.0	11.5		
TEAEs (discontinuation of both drugs in regimen)	14.0	7.7		
Laboratory abnormalities (Grade 3 or 4)	72.0	72.0		
Laboratory abnormalities (Grade 3)	42.0	52.0		
Laboratory abnormalities (Grade 4)	30.0	20.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Died by Day 28

End point title	Percentage of Participants Who Died by Day 28

End point description:

The percentage of participants who died by Day 28 was calculated. Participants in the Full Analysis Set (participants who took at least 1 dose of study drug, and had histologically-confirmed severe alcoholic hepatitis (AH)) with available data were analyzed.

End point type	Secondary

End point timeframe:

Day 28

End point values	Selonsertib + Prednisolone	Placebo + Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	50		
Units: Percentage of participants				
number (not applicable)	4.3	4.0		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Selonsertib + Prednisolone v Placebo + Prednisolone
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [2]
Method	Fisher exact

Notes:

[2] - P-value from 2-sided Fisher's exact test was used to explore differences between treatment groups in the percentage of participants with an event.

Secondary: Percentage of Participants Who Died by Week 8

End point title	Percentage of Participants Who Died by Week 8

End point description:

The percentage of participants who died by Week 8 was calculated. Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Week 8

End point values	Selonsertib + Prednisolone	Placebo + Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	49		
Units: Percentage of participants				
number (not applicable)	20.5	6.1		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Selonsertib + Prednisolone v Placebo + Prednisolone
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.061 [3]
Method	Fisher exact

Notes:

[3] - P-value from 2-sided Fisher's exact test was used to explore differences between treatment groups in the percentage of participants with an event.

Secondary: Percentage of Participants Who Died by Week 12

End point title	Percentage of Participants Who Died by Week 12

End point description:

The percentage of participants who died by Week 12 was calculated. Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Week 12

End point values	Selonsertib + Prednisolone	Placebo + Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	49		
Units: Percentage of participants				
number (not applicable)	25.6	10.2		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Selonsertib + Prednisolone v Placebo + Prednisolone
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.06 [4]
Method	Fisher exact

Notes:

[4] - P-value from 2-sided Fisher's exact test was used to explore differences between treatment groups in the percentage of participants with an event.

Secondary: Percentage of Participants Who Died by Week 24

End point title	Percentage of Participants Who Died by Week 24

End point description:

The percentage of participants who died by Week 24 was calculated. Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Week 24

End point values	Selonsertib + Prednisolone	Placebo + Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	48		
Units: Percentage of participants				
number (not applicable)	31.7	18.8		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Selonsertib + Prednisolone v Placebo + Prednisolone
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.22 [5]
Method	Fisher exact

Notes:

[5] - P-value from 2-sided Fisher's exact test was used to explore differences between treatment groups in the percentage of participants with an event.

Secondary: Percentage of Participants Who Received a Liver Transplant

End point title	Percentage of Participants Who Received a Liver Transplant

End point description:

The percentage of participants who received a liver transplant by week 24 was calculcated. Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Up to 24 weeks

End point values	Selonsertib + Prednisolone	Placebo + Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	48		
Units: Percentage of participants				
number (not applicable)				
Day 28 (n= 45, 48)	2.2	0		
Week 8 (n= 36, 46)	2.8	0		
Week 12 (n= 33, 44)	3.0	0		
Week 24 (n=29, 39)	6.9	2.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Hepatorenal Syndrome (HRS)

End point title	Percentage of Participants With Hepatorenal Syndrome (HRS)

End point description:

The occurrence of HRS was confirmed based on the following diagnostic criteria from the International Ascites Club (IAC): 1) Cirrhosis with ascites, 2) Diagnosis of acute kidney injury (AKI) according to the ICA-AKI criteria, 3) Absence of shock, 4) No current or recent treatment with nephrotoxic drugs, and 5) Absence of parenchymal renal disease as indicated by proteinuria >500 mg/day, microhematuria (> 50 red blood cells per high power field) and/or abnormal renal ultrasonography. Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Up to 24 weeks

End point values	Selonsertib + Prednisolone	Placebo + Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	51		
Units: Percentage of participants				
number (not applicable)	4.2	2.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Infection

End point title	Percentage of Participants With Infection

End point description:

The occurrence of bacterial, fungal, or viral infections was recorded. An infection was considered definite in participants with clinical evidence of infection and a positive culture from a normally sterile source (with the exception of spontaneous bacterial peritonitis). Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Up to 24 weeks

End point values	Selonsertib + Prednisolone	Placebo + Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	51		
Units: Percentage of participants				
number (not applicable)	37.5	29.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Length of Hospital Stay

End point title	Length of Hospital Stay

End point description:

Length of initial hospital stay from first dose date of study drug was calculated for participants who were released from initial hospitalization separately from those who died during their initial hospitalization. Participants in the Full Analysis Set with available data were analyzed. Participants released from initial hospitalization and those who died during initial hospitalization were analyzed separately, so a total of 41 participants and 45 participants were analyzed for the Selonsertib + Prednisolone and Placebo + Prednisolone arms, respectively.

End point type	Secondary

End point timeframe:

Up to 24 weeks

End point values	Selonsertib + Prednisolone	Placebo + Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	45		
Units: Days				
arithmetic mean (standard deviation)				
Released from initial hospitalization (n= 38, 43)	11.0 (± 11.53)	11.0 (± 11.25)		
Died during initial hospitalization (n=3, 2)	36.0 (± 18.52)	6.0 (± 1.41)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Liver Biochemistry Tests: Alanine Aminotransferase (ALT)

End point title	Change From Baseline in Liver Biochemistry Tests: Alanine Aminotransferase (ALT)

End point description:

Change from Baseline was calculated as the value at endpoint minus the value at Baseline.Participants in the Full Analysis Set with available baseline and any postbaseline data were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and up to 24 weeks

End point values	Selonsertib + Prednisolone	Placebo + Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	49		
Units: U/L				
arithmetic mean (standard deviation)				
Change at Week 1 (n= 45, 47)	26 (± 40.7)	29 (± 28.2)		
Change at Week 2 (n= 42, 46)	31 (± 35.0)	36 (± 33.6)		
Change at Week 3 (n= 39, 46)	24 (± 32.6)	24 (± 28.8)		
Change at Week 4 (n= 35, 46)	15 (± 28.7)	12 (± 32.6)		
Change at Week 6 (n= 32, 40)	-10 (± 19.9)	-18 (± 21.8)		
Change at Week 8 (n= 30, 42)	-13 (± 18.1)	-20 (± 24.6)		
Change at Week 12 (n= 27, 39)	-15 (± 19.3)	-17 (± 42.9)		
Change at Week 16 (n= 28, 36)	-14 (± 21.0)	-21 (± 28.6)		
Change at Week 20 (n= 24, 35)	-12 (± 18.6)	-24 (± 21.7)		
Change at Week 24 (n= 25, 35)	-12 (± 19.4)	-22 (± 21.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Liver Biochemistry Tests: Aspartate Aminotransferase (AST)

End point title	Change from Baseline in Liver Biochemistry Tests: Aspartate Aminotransferase (AST)

End point description:

Change from Baseline was calculated as the value at endpoint minus the value at Baseline. Participants in the Full Analysis Set with available baseline and any postbaseline data were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and up to 24 weeks

End point values	Selonsertib + Prednisolone	Placebo + Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	49		
Units: U/L				
arithmetic mean (standard deviation)				
Change at Week 1 (n= 45, 45)	-2 (± 66.9)	4 (± 52.8)		
Change at Week 2 (n= 40, 43)	-17 (± 58.5)	-11 (± 52.9)		
Change at Week 3 (n= 39, 45)	-34 (± 38.4)	-39 (± 54.0)		
Change at Week 4 (n= 35, 44)	-45 (± 35.8)	-55 (± 60.2)		
Change at Week 6 (n= 32, 40)	-54 (± 45.6)	-74 (± 60.0)		
Change at Week 8 (n= 30, 42)	-48 (± 46.6)	-61 (± 63.5)		
Change at Week 12 (n= 27, 37)	-59 (± 45.2)	-63 (± 86.5)		
Change at Week 16 (n= 26, 36)	-59 (± 56.9)	-70 (± 76.4)		
Change at Week 20 (n= 24, 35)	-57 (± 46.9)	-64 (± 72.6)		
Change at Week 24 (n= 25, 35)	-59 (± 49.6)	-68 (± 59.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Liver Biochemistry Tests: Gamma Glutamyl Transferase (GGT)

End point title	Change from Baseline in Liver Biochemistry Tests: Gamma Glutamyl Transferase (GGT)

End point description:

Change from Baseline was calculated as the value at endpoint minus the value at Baseline. Participants in the Full Analysis Set with available baseline and any postbaseline data were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and up to 24 weeks

End point values	Selonsertib + Prednisolone	Placebo + Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	33		
Units: U/L				
arithmetic mean (standard deviation)				
Change at Week 1 (n= 26, 31)	3 (± 79.2)	-1 (± 192.5)		
Change at Week 2 (n= 26, 31)	9 (± 140.8)	9 (± 189.0)		
Change at Week 3 (n= 24, 32)	-12 (± 170.2)	9 (± 197.1)		
Change at Week 4 (n= 25, 30)	-7 (± 169.3)	-5 (± 284.0)		
Change at Week 6 (n= 22, 26)	-61 (± 139.7)	-72 (± 173.4)		

Change at Week 8 (n= 22, 29)	-96 (± 137.7)	-121 (± 314.2)		
Change at Week 12 (n= 20, 26)	-105 (± 136.1)	-100 (± 274.0)		
Change at Week 16 (n= 20, 23)	-87 (± 157.4)	-114 (± 251.3)		
Change at Week 20 (n= 18, 24)	-134 (± 150.9)	-85 (± 342.9)		
Change at Week 24 (n= 20, 25)	-131 (± 154.4)	-54 (± 277.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Liver Biochemistry Tests: Alkaline Phosphatase

End point title	Change from Baseline in Liver Biochemistry Tests: Alkaline Phosphatase

End point description:

Change from Baseline was calculated as the value at endpoint minus the value at Baseline. Participants in the Full Analysis Set with available baseline and any postbaseline data were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and up to 24 weeks

End point values	Selonsertib + Prednisolone	Placebo + Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	49		
Units: U/L				
arithmetic mean (standard deviation)				
Change at Week 1 (n= 45, 47)	11 (± 55.3)	-3 (± 63.6)		
Change at Week 2 (n= 42, 46)	23 (± 70.7)	-5 (± 70.6)		
Change at Week 3 (n= 39, 46)	10 (± 68.7)	-4 (± 89.8)		
Change at Week 4 (n= 35, 46)	8 (± 71.7)	-16 (± 89.8)		
Change at Week 6 (n= 34, 40)	1 (± 65.3)	-21 (± 69.8)		
Change at Week 8 (n= 30, 42)	-14 (± 52.6)	-47 (± 97.8)		
Change at Week 12 (n= 27, 40)	-35 (± 65.0)	-52 (± 102.8)		
Change at Week 16 (n= 28, 36)	-26 (± 83.1)	-50 (± 92.8)		
Change at Week 20 (n= 24, 35)	-29 (± 83.3)	-45 (± 106.8)		
Change at Week 24 (n= 25, 36)	-25 (± 87.3)	-43 (± 101.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Liver Biochemistry Tests: Bilirubin

End point title	Change from Baseline in Liver Biochemistry Tests: Bilirubin

End point description:

Change from Baseline was calculated as the value at endpoint minus the value at Baseline. Participants in the Full Analysis Set with available baseline and any postbaseline data were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and up to 24 weeks

End point values	Selonsertib + Prednisolone	Placebo + Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	49		
Units: mg/dL				
arithmetic mean (standard deviation)				
Change at Week 1 (n= 44, 47)	-2.1 (± 3.99)	-4.3 (± 3.46)		
Change at Week 2 (n= 42, 46)	-2.9 (± 5.34)	-6.3 (± 4.99)		
Change at Week 3 (n= 39, 46)	-4.8 (± 7.68)	-7.2 (± 6.21)		
Change at Week 4 (n= 35, 46)	-6.3 (± 6.01)	-8.6 (± 6.52)		
Change at Week 6 (n= 32, 40)	-8.7 (± 8.22)	-9.3 (± 7.40)		
Change at Week 8 (n= 30, 42)	-8.4 (± 7.53)	-10.3 (± 7.36)		
Change at Week 12 (n= 27, 40)	-9.5 (± 7.86)	-11.2 (± 7.79)		
Change at Week 16 (n= 28, 36)	-9.4 (± 8.35)	-11.3 (± 8.37)		
Change at Week 20 (n= 24, 35)	-8.1 (± 9.88)	-11.3 (± 7.94)		
Change at Week 24 (n= 25, 36)	-9.4 (± 7.72)	-10.7 (± 8.09)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Liver Biochemistry Tests: Albumin

End point title	Change from Baseline in Liver Biochemistry Tests: Albumin

End point description:

Change from Baseline was calculated as the value at endpoint minus the value at Baseline. Participants in the Full Analysis Set with available baseline and any postbaseline data were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and up to 24 weeks

End point values	Selonsertib + Prednisolone	Placebo + Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	49		
Units: g/dL				
arithmetic mean (standard deviation)				
Change at Week 1 (n= 45, 47)	0.2 (± 0.45)	0.2 (± 0.31)		
Change at Week 2 (n= 42, 46)	0.3 (± 0.47)	0.4 (± 0.45)		
Change at Week 3 (n= 39, 46)	0.3 (± 0.58)	0.4 (± 0.54)		
Change at Week 4 (n= 35, 46)	0.4 (± 0.63)	0.5 (± 0.57)		
Change at Week 6 (n= 34, 40)	0.2 (± 0.82)	0.4 (± 0.67)		
Change at Week 8 (n= 30, 42)	0.3 (± 0.80)	0.6 (± 0.66)		
Change at Week 12 (n= 27, 40)	0.5 (± 0.82)	0.6 (± 0.68)		
Change at Week 16 (n= 28, 36)	0.5 (± 0.95)	0.7 (± 0.64)		
Change at Week 20 (n= 24, 35)	0.8 (± 0.92)	0.8 (± 0.68)		
Change at Week 24 (n= 25, 36)	0.8 (± 0.76)	0.8 (± 0.68)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Liver Biochemistry Tests: International Normalized Ratio (INR)

End point title	Change from Baseline in Liver Biochemistry Tests: International Normalized Ratio (INR)

End point description:

Change from Baseline was calculated as the value at endpoint minus the value at Baseline. Participants in the Full Analysis Set with available baseline and any postbaseline data were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and up to 24 weeks

End point values	Selonsertib + Prednisolone	Placebo + Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	49		
Units: Ratio				
arithmetic mean (standard deviation)				
Change at Week 1 (n= 42, 47)	-0.1 (± 0.28)	-0.1 (± 0.16)		
Change at Week 2 (n= 39, 45)	-0.2 (± 0.32)	-0.2 (± 0.23)		
Change at Week 3 (n= 34, 43)	-0.3 (± 0.38)	-0.2 (± 0.25)		
Change at Week 4 (n= 33, 46)	-0.3 (± 0.36)	-0.2 (± 0.18)		
Change at Week 6 (n= 31, 40)	-0.2 (± 0.40)	-0.2 (± 0.33)		
Change at Week 8 (n= 26, 42)	-0.3 (± 0.43)	-0.3 (± 0.19)		
Change at Week 12 (n= 23, 40)	-0.3 (± 0.41)	-0.3 (± 0.19)		
Change at Week 16 (n= 26, 35)	-0.3 (± 0.40)	-0.3 (± 0.22)		
Change at Week 20 (n= 22, 34)	-0.3 (± 0.42)	-0.3 (± 0.27)		

Change at Week 24 (n= 25, 34)	-0.4 (± 0.36)	-0.3 (± 0.32)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Lille Response (score < 0.45) at Day 7

End point title	Percentage of Participants with Lille Response (score < 0.45) at Day 7

End point description:

The Lille score is a tool used to predict which participants with severe alcoholic hepatitis (AH) were not responding to corticosteroid therapy. It ranges between 0 and 1, with low scores (< 0.16) indicating complete response or positive response to steroids (continue therapy) and high scores (≥ 0.56) indicating no response or poor response to steroids (stop therapy). The Lille score was calculated using baseline factors: age, albumin, total bilirubin, serum creatinine, prothrombin time; and the change in total bilirubin between baseline (Day 1) and Day 7. Lille response was defined as having a Lille score < 0.45. Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Day 7

End point values	Selonsertib + Prednisolone	Placebo + Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	51		
Units: Percentage of participants				
number (not applicable)	77.1	86.3		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Selonsertib + Prednisolone v Placebo + Prednisolone
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3 [6]
Method	Fisher exact

Notes:

[6] - P-value was calculated using the 2-sided Fisher's exact test and was used to explore differences between groups in the percentage of participants with response/non-response.

Secondary: Percentage of Participants with a Lille Null Response (score ≥ 0.56) at Day 7

End point title	Percentage of Participants with a Lille Null Response (score ≥ 0.56) at Day 7

End point description:

The Lille score is a tool used to predict which participants with severe AH were not responding to corticosteroid therapy. It ranges between 0 and 1, with low scores (< 0.16) indicating complete response or positive response to steroids (continue therapy) and high scores (≥ 0.56) indicating no response or poor response to steroids (stop therapy). The Lille score was calculated using baseline factors: age, albumin, total bilirubin, serum creatinine, prothrombin time; and the change in total bilirubin between baseline (Day 1) and Day 7. Lille null response was defined as having a Lille score ≥ 0.56. Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Day 7

End point values	Selonsertib + Prednisolone	Placebo + Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	51		
Units: Percentage of participants				
number (not applicable)	14.6	7.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Lille Score at Day 7 as a Continuous Variable

End point title	Lille Score at Day 7 as a Continuous Variable

End point description:

The Lille score is a tool used to predict which participants with severe AH were not responding to corticosteroid therapy. It ranges between 0 and 1, with low scores (< 0.16) indicating complete response or positive response to steroids (continue therapy) and high scores (≥ 0.56) indicating no response or poor response to steroids (stop therapy). The Lille score was calculated using baseline factors: age, albumin, total bilirubin, serum creatinine, prothrombin time; and the change in total bilirubin between baseline (Day 1) and Day 7. Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Day 7

End point values	Selonsertib + Prednisolone	Placebo + Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	48		
Units: Lille score				
arithmetic mean (standard deviation)	0.254 (± 0.2495)	0.178 (± 0.1534)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Mortality Risk at Month 2 and Month 6: Combined Scoring Including Lille Score at Day 7 and Baseline Model for End-Stage Liver Disease (MELD) Score

End point title	Overall Mortality Risk at Month 2 and Month 6: Combined Scoring Including Lille Score at Day 7 and Baseline Model for End-Stage Liver Disease (MELD) Score

End point description:

The Lille score is a tool used to predict which participants with severe AH were not responding to corticosteroid therapy. It ranges between 0 and 1, with low scores (< 0.16) indicating complete response or positive response to steroids (continue therapy) and high scores (≥ 0.56) indicating no response or poor response to steroids (stop therapy). MELD scores are used to assess prognosis and suitability for liver transplantation. Scores can range from 6 to 40, with higher scores indicating greater disease severity. A scoring system combining the Lille score at Day 7 and the baseline MELD score was used to calculate the percentage of participants expected to die by Month 2 and by Month 6. Participants in the Full Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline and Day 7 Time Points Used to Calculate Overall Mortality Risk at Months 2 and 6

End point values	Selonsertib + Prednisolone	Placebo + Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	48		
Units: Percentage of participants				
arithmetic mean (standard deviation)				
Mortality Risk at Month 2	13.0 (± 10.94)	9.7 (± 6.57)		
Mortality Risk at Month 6	19.8 (± 15.15)	15.2 (± 9.28)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Prognostic Index: Model for End-Stage Liver Disease (MELD) Score

End point title	Change from Baseline in Prognostic Index: Model for End-Stage Liver Disease (MELD) Score

End point description:

MELD scores are used to assess prognosis and suitability for liver transplantation. Scores can range from 6 to 40, with higher scores indicating greater disease severity. Change from Baseline was calculated as the value at endpoint minus the value at Baseline. Participants in the Full Analysis Set with available

baseline and any postbaseline data were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and up to 24 weeks

End point values	Selonsertib + Prednisolone	Placebo + Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	49		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Change at Week 1 (n= 44, 47)	-2 (± 2.9)	-3 (± 2.6)		
Change at Week 2 (n= 42, 45)	-3 (± 4.0)	-5 (± 3.5)		
Change at Week 3 (n= 36, 43)	-4 (± 4.7)	-5 (± 3.9)		
Change at Week 4 (n= 35, 46)	-5 (± 5.2)	-6 (± 3.9)		
Change at Week 6 (n= 32, 39)	-6 (± 6.1)	-7 (± 5.2)		
Change at Week 8 (n= 28, 41)	-7 (± 5.9)	-8 (± 4.7)		
Change at Week 12 (n= 26, 40)	-7 (± 6.0)	-10 (± 4.8)		
Change at Week 16 (n= 29, 35)	-7 (± 6.5)	-9 (± 5.5)		
Change at Week 20 (n= 23, 34)	-8 (± 7.6)	-10 (± 5.4)		
Change at Week 24 (n= 26, 34)	-9 (± 6.1)	-10 (± 5.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Prognostic Index: Child-Pugh-Turcotte (CPT) Score

End point title	Change from Baseline in Prognostic Index: Child-Pugh-Turcotte (CPT) Score

End point description:

CPT scores grade the severity of cirrhosis and are used to determine the need for liver transplantation. Scores can range from 5 to 15, with higher scores indicating a greater severity of disease. Participants in the Full Analysis Set with available baseline and any postbaseline data were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and up to 24 weeks

End point values	Selonsertib + Prednisolone	Placebo + Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	49		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Change at Week 1 (n= 41, 47)	0 (± 1.5)	-1 (± 0.9)		
Change at Week 2 (n= 39, 45)	-1 (± 1.4)	-1 (± 1.4)		
Change at Week 3 (n= 34, 43)	-1 (± 1.7)	-1 (± 1.4)		
Change at Week 4 (n= 33, 46)	-1 (± 1.9)	-2 (± 1.7)		
Change at Week 6 (n= 28, 39)	-1 (± 2.1)	-2 (± 1.7)		
Change at Week 8 (n= 26, 41)	-2 (± 2.4)	-2 (± 1.5)		
Change at Week 12 (n= 23, 40)	-2 (± 2.2)	-3 (± 1.7)		
Change at Week 16 (n= 26, 35)	-2 (± 2.4)	-3 (± 1.8)		
Change at Week 20 (n= 22, 34)	-3 (± 2.3)	-3 (± 1.6)		
Change at Week 24 (n= 24, 34)	-3 (± 1.7)	-3 (± 1.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Prognostic Index: Maddrey Discriminant Function (DF) Score

End point title	Change from Baseline in Prognostic Index: Maddrey Discriminant Function (DF) Score

End point description:

Baseline Maddrey DF score is a prognostic tool used to determine the next step of treatment based on the severity of AH. Maddrey DF score of < 32 indicates mild to moderate AH and a lower chance of death in the next few months. Maddrey DF score of ≥ 32 indicates severe AH and a higher chance of death in the next few months. Participants in the Full Analysis Set with available baseline and any postbaseline data were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and up to 24 weeks

End point values	Selonsertib + Prednisolone	Placebo + Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	49		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Change at Week 1 (n= 39, 47)	-8 (± 15.2)	-10 (± 7.7)		
Change at Week 2 (n= 37, 45)	-13 (± 18.1)	-15 (± 11.4)		
Change at Week 3 (n= 33, 43)	-17 (± 21.8)	-17 (± 13.3)		
Change at Week 4 (n= 31, 46)	-19 (± 20.0)	-19 (± 10.9)		
Change at Week 6 (n= 27, 39)	-20 (± 23.2)	-19 (± 17.6)		
Change at Week 8 (n= 25, 41)	-19 (± 21.5)	-21 (± 12.0)		
Change at Week 12 (n= 22, 40)	-23 (± 21.8)	-23 (± 12.2)		

Change at Week 16 (n= 24, 35)	-23 (± 22.6)	-23 (± 13.7)		
Change at Week 20 (n= 21, 34)	-25 (± 26.2)	-23 (± 15.4)		
Change at Week 24 (n= 23, 34)	-27 (± 21.7)	-22 (± 16.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of Survival at Day 28

End point title	Kaplan-Meier Estimate of Survival at Day 28

End point description:

The Kaplan-Meier (KM) estimate of survival at Day 28 was calculated. Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Day 28

End point values	Selonsertib + Prednisolone	Placebo + Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	51		
Units: Percentage of participants				
number (confidence interval 95%)	95.7 (84.0 to 98.9)	96.1 (85.2 to 99.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of Survival at Week 8

End point title	Kaplan-Meier Estimate of Survival at Week 8

End point description:

The KM estimate of survival at Week 8 was calculated. Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Week 8

End point values	Selonsertib + Prednisolone	Placebo + Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	51		
Units: Percentage of participants				
number (confidence interval 95%)	80.0 (65.1 to 89.1)	94.0 (82.6 to 98.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of Survival at Week 12

End point title	Kaplan-Meier Estimate of Survival at Week 12

End point description:

The KM estimate of survival at Week 12 was calculated. Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Week 12

End point values	Selonsertib + Prednisolone	Placebo + Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	51		
Units: Percentage of participants				
number (confidence interval 95%)	75.3 (59.8 to 85.5)	89.9 (77.5 to 95.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of Survival at Week 24

End point title	Kaplan-Meier Estimate of Survival at Week 24

End point description:

The KM estimate of survival at Week 24 was calculated. Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Week 24

End point values	Selonsertib + Prednisolone	Placebo + Prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	51		
Units: Percentage of participants				
number (confidence interval 95%)	70.3 (54.3 to 81.6)	81.7 (67.7 to 90.0)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Day 28 plus 30 days

Adverse event reporting additional description:

Safety Analysis Set included all participants who were randomized and took at least 1 dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Selonsertib + Prednisolone

Reporting group description:

Participants received selonsertib (GS-4997) 18 mg tablet orally once daily + prednisolone 40 mg (4 x 10 mg tablets) orally once daily for 28 days.

Reporting group title	Placebo + Prednisolone

Reporting group description:

Participants received placebo-to-match selonsertib 18 mg tablet orally once daily + prednisolone 40 mg (4 x 10 mg tablets) orally once daily for 28 days.

Serious adverse events	Selonsertib + Prednisolone	Placebo + Prednisolone	
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 50 (50.00%)	21 / 52 (40.38%)	
number of deaths (all causes)	8	3	
number of deaths resulting from adverse events	8	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 50 (4.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			

subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	2 / 50 (4.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea at rest			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lung disorder			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood lactic acid increased			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Hepatic encephalopathy			
subjects affected / exposed	2 / 50 (4.00%)	5 / 52 (9.62%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma hepatic			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Coagulopathy			
subjects affected / exposed	3 / 50 (6.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 50 (2.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 50 (0.00%)	2 / 52 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abdominal pain lower			

subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer perforation			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoperitoneum			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatobiliary disorders			
Hepatorenal syndrome			

subjects affected / exposed	2 / 50 (4.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 50 (2.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Alcoholic liver disease			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cirrhosis alcoholic			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 50 (4.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	3 / 50 (6.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 50 (2.00%)	2 / 52 (3.85%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 1	
Peritonitis bacterial			
subjects affected / exposed	2 / 50 (4.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Abscess limb			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain abscess			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal abscess central nervous			

system			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Klebsiella infection			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Localised infection			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia legionella			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Staphylococcal sepsis			

subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine infection			
subjects affected / exposed	0 / 50 (0.00%)	1 / 52 (1.92%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection fungal			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 50 (2.00%)	2 / 52 (3.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 52 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Selonsertib + Prednisolone	Placebo + Prednisolone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 50 (86.00%)	42 / 52 (80.77%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	4 / 50 (8.00%)	3 / 52 (5.77%)	
occurrences (all)	4	3	

Nervous system disorders			
Hepatic encephalopathy			
subjects affected / exposed	12 / 50 (24.00%)	7 / 52 (13.46%)	
occurrences (all)	13	9	
Headache			
subjects affected / exposed	1 / 50 (2.00%)	3 / 52 (5.77%)	
occurrences (all)	1	3	
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	4 / 50 (8.00%)	2 / 52 (3.85%)	
occurrences (all)	4	2	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	12 / 50 (24.00%)	11 / 52 (21.15%)	
occurrences (all)	12	12	
Fatigue			
subjects affected / exposed	4 / 50 (8.00%)	6 / 52 (11.54%)	
occurrences (all)	4	6	
Oedema			
subjects affected / exposed	4 / 50 (8.00%)	6 / 52 (11.54%)	
occurrences (all)	4	6	
Asthenia			
subjects affected / exposed	4 / 50 (8.00%)	2 / 52 (3.85%)	
occurrences (all)	4	2	
Pyrexia			
subjects affected / exposed	1 / 50 (2.00%)	4 / 52 (7.69%)	
occurrences (all)	1	5	
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	15 / 50 (30.00%)	14 / 52 (26.92%)	
occurrences (all)	15	14	
Constipation			
subjects affected / exposed	6 / 50 (12.00%)	5 / 52 (9.62%)	
occurrences (all)	6	5	
Diarrhoea			

subjects affected / exposed	4 / 50 (8.00%)	4 / 52 (7.69%)	
occurrences (all)	4	4	
Nausea			
subjects affected / exposed	6 / 50 (12.00%)	2 / 52 (3.85%)	
occurrences (all)	7	2	
Varices oesophageal			
subjects affected / exposed	3 / 50 (6.00%)	4 / 52 (7.69%)	
occurrences (all)	3	4	
Abdominal pain upper			
subjects affected / exposed	4 / 50 (8.00%)	1 / 52 (1.92%)	
occurrences (all)	4	1	
Vomiting			
subjects affected / exposed	4 / 50 (8.00%)	1 / 52 (1.92%)	
occurrences (all)	5	1	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 50 (6.00%)	6 / 52 (11.54%)	
occurrences (all)	3	6	
Epistaxis			
subjects affected / exposed	4 / 50 (8.00%)	2 / 52 (3.85%)	
occurrences (all)	5	2	
Cough			
subjects affected / exposed	2 / 50 (4.00%)	3 / 52 (5.77%)	
occurrences (all)	2	4	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	8 / 50 (16.00%)	4 / 52 (7.69%)	
occurrences (all)	8	4	
Rash			
subjects affected / exposed	2 / 50 (4.00%)	5 / 52 (9.62%)	
occurrences (all)	2	5	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	5 / 50 (10.00%)	5 / 52 (9.62%)	
occurrences (all)	5	5	
Agitation			

subjects affected / exposed	0 / 50 (0.00%)	3 / 52 (5.77%)	
occurrences (all)	0	3	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	5 / 50 (10.00%)	1 / 52 (1.92%)	
occurrences (all)	7	1	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	3 / 50 (6.00%)	4 / 52 (7.69%)	
occurrences (all)	3	4	
Infections and infestations			
Sepsis			
subjects affected / exposed	5 / 50 (10.00%)	0 / 52 (0.00%)	
occurrences (all)	5	0	
Escherichia urinary tract infection			
subjects affected / exposed	3 / 50 (6.00%)	1 / 52 (1.92%)	
occurrences (all)	3	1	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	15 / 50 (30.00%)	1 / 52 (1.92%)	
occurrences (all)	15	1	
Hypokalaemia			
subjects affected / exposed	7 / 50 (14.00%)	4 / 52 (7.69%)	
occurrences (all)	7	4	
Hyperglycaemia			
subjects affected / exposed	4 / 50 (8.00%)	4 / 52 (7.69%)	
occurrences (all)	4	5	
Hypomagnesaemia			
subjects affected / exposed	4 / 50 (8.00%)	3 / 52 (5.77%)	
occurrences (all)	4	3	
Hyperkalaemia			
subjects affected / exposed	1 / 50 (2.00%)	4 / 52 (7.69%)	
occurrences (all)	1	6	
Hypophosphataemia			
subjects affected / exposed	4 / 50 (8.00%)	1 / 52 (1.92%)	
occurrences (all)	4	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 June 2016	-Added 2 inclusion criteria to further define the clinical diagnosis of severe AH -Updated guidance on subject management during the hospitalization period -Removed the interim analysis for decision-making purposes and clarified when the primary analysis would be conducted -Updated data included for Section 1.2.5. Clinical Trials for GS-4997 -Clarified the fixed dosing of PRED (ie, no tapering of the PRED dose) -Updated subject SEL/placebo and PRED stopping rules and a relevant paragraph in the toxicity management section of the protocol -Added adjudication criteria for the evaluation of potential drug-induced liver injury (DILI) -Added trial stopping criteria and clarified the Data
11 January 2017	-Removed information in the Introduction that was included in the current version of the Investigators Brochure -Added data from the GS-US-384-1497 study to the Introduction -Clarified that local laboratory testing results could be used to confirm eligibility; made other clarifications to study procedures throughout -Added mortality assessment at Week 8 as a secondary objective -Added assessment of changes in Fibroscan as an exploratory objective -Updated text related to the Lille score calculation at Day 7 and PRED discontinuation for subjects with a null response at Day 7; added Lille null response as a secondary endpoint -Added FibroScan in subjects without ascites, for sites that have instrument capability, to the study procedures -Added exclusion criteria #10 to exclude subjects with clinical suspicion of pneumonia -Updated exclusion criteria #21 to allow subjects to enroll if systemic corticosteroids were started 3 or fewer days before baseline/Day 1 -Updated exclusion criteria #22 to remove the prohibition of CYP3A4 inhibitors. Strong CYP3A4 inducers continued to be disallowed. -Added standardized treatment guidelines for sepsis -Provided guidance for the treatment of pneumonia infections -Added text to allow subjects to be randomized and stratified by MELD score based on local laboratory testing -Included additional biomarkers for future assessments -Clarified reporting periods for nonserious adverse events (AEs) and serious adverse events (SAEs) -Provided guidance on PRED dose reduction or interruption
04 August 2017	-Inserted updated information on efficacy results from previous clinical trials in Section 1 -HepQuant testing and all references to the HepQuant substudy were removed from the protocol. -Clarified use of chest x-ray, HBV, HCV, HIV serology, and urine drug testing to allow results (including hospital transfers) within 10 days of screening to determine eligibility -Added language regarding re-screening of subjects -Clarified posttreatment visit requirements for subjects prematurely discontinued from both study drugs -Clarified liver biopsy requirement regarding inadequate biopsy samples that do not suggest an alternative diagnosis to AH -Clarified PK language regarding dialysis and subjects on renal replacement therapy -Changed ALT/AST stopping criteria to exclude > 5 x postbaseline nadir for ALT and AST; and allowed for investigator discretion if there is an alternative cause -Clarified Lille score parameters for study drug discontinuation -Updated Appendix 2 to provide further clarification on certain study procedures

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported