Clinical trial results:
TRANSFORM: A 24-week, Randomized, Placebo-controlled, Double-blind, Phase 2b Trial of Setanaxib in Patients with Primary Biliary Cholangitis (PBC) and Elevated Liver Stiffness

Summary

EudraCT number	2021-001810-13
Trial protocol	HU DE AT FR ES PL IT GR SE CZ BE
Global end of trial date	02 July 2024

Results information

Result version number	v1 (current)
This version publication date	04 April 2025
First version publication date	04 April 2025

Trial information

Trial identification

Sponsor protocol code	GSN000350

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05014672
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 132135

Notes:

Sponsors

Sponsor organisation name	Calliditas Therapeutics Suisse SA
Sponsor organisation address	Chemin des Aulx 14, Plan-les-Ouates, Switzerland, 1228
Public contact	Head of Clinical Operations, Calliditas Therapeutics AB, +46 84113005, info@calliditas.com
Scientific contact	Head of Clinical Operations, Calliditas Therapeutics AB, info@calliditas.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	29 July 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 July 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of setanaxib on ALP at Week 24 in patients with PBC and with elevated liver stiffness and intolerance or inadequate response to UDCA

Protection of trial subjects:

An Independent Data Monitoring Committee (IDMC) was established to oversee the safety of participating patients. The IDMC met regularly to review unblinded safety data. The IDMC could recommend change(s) to the setanaxib dose regimen(s), or interruption or discontinuation of an active treatment group(s) based on the regular IDMC safety data reviews. The role and responsibilities of the IDMC and frequency of review are outlined in the IDMC Charter.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 February 2022
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	Poland: 3
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Czechia: 3
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	New Zealand: 2
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	United States: 18
Worldwide total number of subjects	76
EEA total number of subjects	31

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)	61
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

178 patients were screened. 101 patients failed screening.

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, Monitor, Data analyst

Arms

Are arms mutually exclusive?	No
Arm title	Setanaxib 1200 mg/Day

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Setanaxib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants will be administered setanaxib at a dose of 1200 mg/day for the 24-week double-blind treatment period.
Setanaxib: Oral tablets, 400mg per tablet

Arm title	Setanaxib 1600 mg/Day

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Setanaxib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants will be administered setanaxib at a dose of 1600 mg/day for the 24-week double-blind treatment period.
Setanaxib: Oral tablets, 400mg per tablet

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants will be administered a placebo for the 24-week double-blind treatment period.
Placebo: Oral tablets

Arm title	Setanaxib 1200 mg/Day or 1600 mg/Day

Arm description:

Arm added to be able to enter results for the secondary endpoints where setanaxib doses are combined

Arm type	Experimental
Investigational medicinal product name	Setanaxib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants will be administered setanaxib at a dose of 1200 mg/day or 1600 mg/Day for the 24-week double-blind treatment period.
Setanaxib: Oral tablets, 400mg per tablet

Number of subjects in period 1	Setanaxib 1200 mg/Day	Setanaxib 1600 mg/Day	Placebo
Started	24	25	27
Completed	18	20	23
Not completed	6	5	4
Consent withdrawn by subject	3	-	3
Physician decision	-	1	-
Adverse event, non-fatal	2	3	-
Patient removed at Sponsor request	-	1	1
Protocol deviation	1	-	-

Number of subjects in period 1	Setanaxib 1200 mg/Day or 1600 mg/Day
Started	49
Completed	38
Not completed	11
Consent withdrawn by subject	3
Physician decision	1
Adverse event, non-fatal	5
Patient removed at Sponsor request	1
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Setanaxib 1200 mg/Day
Reporting group description: -	
Reporting group title	Setanaxib 1600 mg/Day
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Setanaxib 1200 mg/Day or 1600 mg/Day
Reporting group description:	
Arm added to be able to enter results for the secondary endpoints where setanaxib doses are combined	

Reporting group values	Setanaxib 1200 mg/Day	Setanaxib 1600 mg/Day	Placebo
Number of subjects	24	25	27
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	18	18	25
From 65-84 years	6	7	2
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	22	24	25
Male	2	1	2
Randomised Screening serum ALP strata			
ALP=alkaline phosphatase; ULN=upper limit of normal			
Units: Subjects			
< 3.0 × ULN	18	18	18
≥ 3.0 × ULN	6	7	9

Reporting group values	Setanaxib 1200 mg/Day or 1600 mg/Day	Total	
Number of subjects	49	76	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	

Adolescents (12-17 years)	0	0	
Adults (18-64 years)	36	61	
From 65-84 years	13	15	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	46	71	
Male	3	5	
Randomised Screening serum ALP strata			
ALP=alkaline phosphatase; ULN=upper limit of normal			
Units: Subjects			
< 3.0 × ULN	36	54	
≥ 3.0 × ULN	13	22	

Subject analysis sets

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS) included all patients who received at least 1 tablet of IMP or placebo during the randomised part of the study and had at least 1 post-Baseline ALP value for the primary endpoint. Patients were analysed based on the treatment group they were randomised to regardless of the actual treatment received. The FAS was used for summaries of Baseline and efficacy data.

Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Analysis Set (SS) included all randomised patients who received at least 1 tablet of IMP or placebo. Patients included were analysed based on actual treatment initially received.

Reporting group values	Full Analysis Set	Safety Analysis Set	
Number of subjects	76	76	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	61	61	
From 65-84 years	15	15	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	71	71	
Male	5	5	
Randomised Screening serum ALP strata			
ALP=alkaline phosphatase; ULN=upper limit of normal			
Units: Subjects			
< 3.0 × ULN	54	54	
≥ 3.0 × ULN	22	22	

End points

End points reporting groups

Reporting group title	Setanaxib 1200 mg/Day
Reporting group description: -	
Reporting group title	Setanaxib 1600 mg/Day
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Setanaxib 1200 mg/Day or 1600 mg/Day

Reporting group description:

Arm added to be able to enter results for the secondary endpoints where setanaxib doses are combined

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS) included all patients who received at least 1 tablet of IMP or placebo during the randomised part of the study and had at least 1 post-Baseline ALP value for the primary endpoint. Patients were analysed based on the treatment group they were randomised to regardless of the actual treatment received. The FAS was used for summaries of Baseline and efficacy data.

Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Analysis Set (SS) included all randomised patients who received at least 1 tablet of IMP or placebo. Patients included were analysed based on actual treatment initially received.

Primary: Change in ALP at Week 24 Compared to Baseline

End point title	Change in ALP at Week 24 Compared to Baseline[1]

End point description:

Change in ALP (%) at Week 24 Compared to Baseline

End point type	Primary

End point timeframe:

Baseline (Day 1) and Week 24

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Combined doses and separate doses are reported as separate endpoints per study protocol.

End point values	Setanaxib 1200 mg/Day	Setanaxib 1600 mg/Day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	25	27	
Units: ratio				
geometric mean (confidence interval 95%)	0.89 (0.802 to 0.988)	0.84 (0.758 to 0.931)	1.03 (0.936 to 1.141)	

Statistical analyses

Statistical analysis title	Change in ALP at Week 24 Compared to Baseline
Comparison groups	Setanaxib 1200 mg/Day v Placebo

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0206
Method	Mixed Model Repeated Measures
Parameter estimate	Ratio of geometric LS mean vs placebo
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.746
upper limit	0.994

Statistical analysis title	Change in ALP at Week 24 Compared to Baseline
Comparison groups	Setanaxib 1600 mg/Day v Placebo
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0057
Method	Mixed Model Repeated Measures
Parameter estimate	Ratio of geometric LS mean vs placebo
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.703
upper limit	0.939

Secondary: Change in Fatigue at Week 24 Compared to Baseline, as Assessed by the PROMIS Short Form-Fatigue 7b Daily

End point title	Change in Fatigue at Week 24 Compared to Baseline, as Assessed by the PROMIS Short Form-Fatigue 7b Daily[2]

End point description:

The Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue Short Form 7b measures the severity of fatigue since waking. There are 7 questions, each scored between 1 and 5, with a total score between 7 to 35. A higher score indicates worse fatigue. This raw score is converted to a T score (a standardized score with a mean of 50 and a SD of 10.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 24

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Combined doses and separate doses are reported as separate endpoints per study protocol.

End point values	Setanaxib 1200 mg/Day	Setanaxib 1600 mg/Day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	18	18	
Units: units on a scale				
least squares mean (confidence interval 95%)	-3.60 (-7.625 to 0.429)	-0.80 (-4.679 to 3.072)	-1.43 (-5.331 to 2.461)	

Statistical analyses

Statistical analysis title	Fatigue at Week 24 PROMIS Short Form-Fatigue 7b
Comparison groups	Setanaxib 1200 mg/Day v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2214
Method	Mixed Model Repeated Measures
Parameter estimate	LS mean difference vs placebo
Point estimate	-2.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.785
upper limit	3.458

Statistical analysis title	Fatigue at Week 24 PROMIS Short Form-Fatigue 7b
Comparison groups	Setanaxib 1600 mg/Day v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.591
Method	Mixed Model Repeated Measures
Parameter estimate	LS mean difference vs placebo
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.859
upper limit	6.12

Secondary: Change in Fatigue at Week 24 Compared to Baseline, as Assessed by the Patient's Global Impression of Severity (PGIS) Fatigue

End point title	Change in Fatigue at Week 24 Compared to Baseline, as Assessed by the Patient's Global Impression of Severity (PGIS) Fatigue[3]

End point description:

The Patient's Global Impression of Severity (PGIS)-Fatigue is a global index where subjects are asked to rate the severity of fatigue on a 5-point scale within the past 7 days, with choices of 1=None, 2=Mild, 3=Moderate, 4=Severe and 5=Very Severe. Higher scores indicate a worse assessment for fatigue.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 24

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Combined doses and separate doses are reported as separate endpoints per study protocol.

End point values	Setanaxib 1200 mg/Day	Setanaxib 1600 mg/Day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	17	18	
Units: units on a scale				
arithmetic mean (standard deviation)	-0.07 (± 0.730)	0.12 (± 0.857)	0.22 (± 1.003)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Fatigue at Week 24 Compared to Baseline, as Assessed by the Patient’s Global Impression of Change (PGIC) Fatigue

End point title	Change in Fatigue at Week 24 Compared to Baseline, as Assessed by the Patient’s Global Impression of Change (PGIC) Fatigue[4]

End point description:

The Patient's Global Impression of Change (PGIC)-Fatigue is a 7-point scale reflecting a subject's rating of overall improvement where subjects are asked to rate their overall improvement with fatigue with 1=Very much improved, 2=Much improved, 3=Minimally improved, 4=No change, 5=Worse, 6=Much worse, 7=Very much worse. Higher scores indicate a worse outcome for change in fatigue.

End point type	Secondary

End point timeframe:

Week 24

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Combined doses and separate doses are reported as separate endpoints per study protocol.

End point values	Setanaxib 1200 mg/Day	Setanaxib 1600 mg/Day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	21	19	
Units: units on a scale				
arithmetic mean (standard deviation)	3.27 (± 1.534)	3.62 (± 1.564)	3.58 (± 1.427)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Fatigue at Week 24 Compared to Baseline, as Assessed by the PBC-40 Questionnaire (PBC 40) Fatigue Domain

End point title	Change in Fatigue at Week 24 Compared to Baseline, as Assessed by the PBC-40 Questionnaire (PBC 40) Fatigue Domain[5]

End point description:

PBC-40 fatigue domain includes 11 item questions, items scores range from 1 to 5. The individual item scores are summed to obtain a total domain score (Range for fatigue domain: 11 to 55), high scores represent high impact and low scores indicate low impact of PBC on the quality of life.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 24

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Combined doses and separate doses are reported as separate endpoints per study protocol.

End point values	Setanaxib 1200 mg/Day	Setanaxib 1600 mg/Day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	23	25	
Units: units on a scale				
least squares mean (confidence interval 95%)	-1.44 (-4.919 to 2.048)	-1.83 (-5.361 to 1.699)	-1.85 (-5.217 to 1.515)	

Statistical analyses

Statistical analysis title	Change in Fatigue at Week 24 by the PBC-40
Comparison groups	Setanaxib 1200 mg/Day v Placebo
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5675
Method	Mixed Model Repeated Measures
Parameter estimate	LS mean difference vs placebo
Point estimate	0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.454
upper limit	5.285

Statistical analysis title	Change in Fatigue at Week 24 by the PBC-40
Comparison groups	Setanaxib 1600 mg/Day v Placebo

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5032
Method	Mixed Model Repeated Measures
Parameter estimate	LS mean difference vs placebo
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.886
upper limit	4.926

Secondary: Change in Liver Stiffness at Week 24 Compared to Screening

End point title	Change in Liver Stiffness at Week 24 Compared to Screening[6]

End point description:

Change in liver stiffness at Week 24 compared to Screening, as assessed by transient elastography (FibroScan®)

End point type	Secondary

End point timeframe:

Screening (Day -28) and Week 24

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Combined doses and separate doses are reported as separate endpoints per study protocol.

End point values	Setanaxib 1200 mg/Day	Setanaxib 1600 mg/Day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	25	27	
Units: ratio				
least squares mean (confidence interval 95%)	0.78 (0.672 to 0.906)	0.88 (0.764 to 1.012)	0.92 (0.808 to 1.055)	

Statistical analyses

Statistical analysis title	Change in Liver Stiffness at Week 24
Comparison groups	Setanaxib 1200 mg/Day v Placebo
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0491
Method	Mixed Model Repeated Measures
Parameter estimate	Ratio of geometric LS mean vs placebo
Point estimate	0.85

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.692
upper limit	1.033

Statistical analysis title	Copy of Change in Liver Stiffness at Week 24
Comparison groups	Setanaxib 1600 mg/Day v Placebo
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3099
Method	Mixed Model Repeated Measures
Parameter estimate	Ratio of geometric LS mean vs placebo
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.783
upper limit	1.158

Secondary: Change in Pruritus at Week 24 Compared to Baseline, as Assessed by the Worst Itch Numerical Rating Scale (WI-NRS)

End point title	Change in Pruritus at Week 24 Compared to Baseline, as Assessed by the Worst Itch Numerical Rating Scale (WI-NRS)[7]

End point description:

WI-NRS is a daily patient-reported measure of itch intensity using an 11-point scale where 0=no itch and 10=worst itching imaginable. The WI-NRS score is calculated by averaging the daily WI-NRS scores before the visit date (inclusive). Higher scores indicate worse functioning for pruritus on the WI-NRS.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 24

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Combined doses and separate doses are reported as separate endpoints per study protocol.

End point values	Setanaxib 1200 mg/Day	Setanaxib 1600 mg/Day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	15	16	
Units: units on a scale				
arithmetic mean (standard deviation)	-0.23 (± 2.280)	0.61 (± 1.391)	-0.56 (± 2.268)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Pruritus at Week 24 Compared to Baseline, as Assessed by the PBC-40 Itch Domain

End point title	Change in Pruritus at Week 24 Compared to Baseline, as Assessed by the PBC-40 Itch Domain[8]

End point description:

Pruritus was assessed by answering 3 questions on the PBC-40 Itch domain from 1 to 5, which was also summed to obtain a total domain score (range 3 to 15). A high score represents a high impact, and a low score indicates low impact of pruritus on the quality of life.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 24

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Combined doses and separate doses are reported as separate endpoints per study protocol.

End point values	Setanaxib 1200 mg/Day	Setanaxib 1600 mg/Day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	19	20	
Units: units on a scale				
arithmetic mean (standard deviation)	-1.11 (± 2.111)	0.32 (± 2.647)	-0.70 (± 3.114)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Pruritus at Week 24 Compared to Baseline, as Assessed by the PGIS Pruritus

End point title	Change in Pruritus at Week 24 Compared to Baseline, as Assessed by the PGIS Pruritus[9]

End point description:

PGIS-Pruritus is a global index where subjects are asked to rate the severity of pruritus on a 5-point scale within the past 7 days, with choices of 1=None, 2=Mild, 3=Moderate, 4=Severe and 5=Very Severe. Higher scores indicate a worse assessment for pruritus.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 24

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Combined doses and separate doses are reported as separate endpoints per study protocol.

End point values	Setanaxib 1200 mg/Day	Setanaxib 1600 mg/Day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	16	18	
Units: units on a scale				
arithmetic mean (standard deviation)	-0.50 (± 0.941)	0.25 (± 0.775)	-0.11 (± 0.758)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Pruritus at Week 24 Compared to Baseline, as Assessed by the PGIC Pruritus

End point title	Change in Pruritus at Week 24 Compared to Baseline, as Assessed by the PGIC Pruritus[10]

End point description:

The PGIC-Pruritus is a 7-point scale reflecting a subject's rating of overall improvement where subjects are asked to rate their overall improvement with fatigue with 1=Very much improved, 2=Much improved, 3=Minimally improved, 4=No change, 5=Worse, 6=Much worse, 7=Very much worse. Higher scores indicate a worse outcome for change in pruritus.

End point type	Secondary

End point timeframe:

Week 24

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Combined doses and separate doses are reported as separate endpoints per study protocol.

End point values	Setanaxib 1200 mg/Day	Setanaxib 1600 mg/Day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	21	19	
Units: units on a scale				
arithmetic mean (standard deviation)	2.73 (± 1.751)	3.38 (± 1.244)	3.37 (± 1.535)	

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in Markers of Cholestasis at Week 24

End point title	Changes in Markers of Cholestasis at Week 24[11]

End point description:

Changes in markers of cholestasis as assessed by proportion of patients at Week 24 with:
-ALP reduction to <1.67×ULN and total bilirubin ≤1×ULN and a ≥15% or ≥30% or ≥40% or ≥70% ALP reduction from Baseline, respectively
-ALP reduction to <1.5×ULN and total bilirubin ≤1×ULN and a ≥40% ALP reduction from Baseline
-ALP <1×ULN and total bilirubin ≤1×ULN
-Total bilirubin <0.6×ULN

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 24

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Combined doses and separate doses are reported as separate endpoints per study protocol.

End point values	Setanaxib 1200 mg/Day	Setanaxib 1600 mg/Day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	24	25	27	
Units: participants				
ALP <1.67×ULN & tot bili ≤1×ULN and ≥15% ALP red.	1	4	1	
ALP <1.67×ULN & tot bili ≤1×ULN and ≥30% ALP red.	1	2	0	
ALP <1.67×ULN & tot bili ≤1×ULN and ≥40% ALP red.	0	2	0	
ALP <1.67×ULN & tot bili ≤1×ULN and ≥70% ALP red.	0	0	0	
ALP <1.50×ULN & tot bili ≤1×ULN and ≥40% ALP red.	0	2	0	
ALP <1.00×ULN and Total Bilirubin ≤1×ULN	0	1	0	
Total bilirubin <0.6×ULN	19	18	19	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in ALP at Week 24 Compared to Baseline, Where Setanaxib Doses Are Combined

End point title	Change in ALP at Week 24 Compared to Baseline, Where Setanaxib Doses Are Combined[12]

End point description:

Change in ALP (%) at Week 24 Compared to Baseline, where setanaxib doses are combined

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 24

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Combined doses and separate doses are reported as separate endpoints per study protocol.

End point values	Placebo	Setanaxib 1200 mg/Day or 1600 mg/Day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	49		
Units: ratio				
least squares mean (confidence interval 95%)	1.03 (0.930 to 1.135)	0.87 (0.804 to 0.931)		

Statistical analyses

Statistical analysis title	Change in ALP at Week 24 Setanaxib Doses Combined
Comparison groups	Setanaxib 1200 mg/Day or 1600 mg/Day v Placebo
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0039
Method	Mixed Model Repeated Measures
Parameter estimate	Ratio of geometric LS mean vs placebo
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.743
upper limit	0.954

Secondary: Change in Fatigue at Week 24 Compared to Baseline, as Assessed by the PROMIS Short Form-Fatigue 7b Daily, Where Setanaxib Doses Are Combined

End point title	Change in Fatigue at Week 24 Compared to Baseline, as Assessed by the PROMIS Short Form-Fatigue 7b Daily, Where Setanaxib Doses Are Combined[13]

End point description:

The Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue Short Form 7b measures the severity of fatigue since waking. There are 7 questions, each scored between 1 and 5, with a total score between 7 to 35. A higher score indicates worse fatigue. This raw score is converted to a T score (a standardized score with a mean of 50 and a SD of 10.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 24

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Combined doses and separate doses are reported as separate endpoints per study protocol.

End point values	Placebo	Setanaxib 1200 mg/Day or 1600 mg/Day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	38		
Units: units on a scale				
least squares mean (confidence interval 95%)	-1.45 (-5.372 to 2.467)	-2.12 (-4.925 to 0.678)		

Statistical analyses

Statistical analysis title	Change in Fatigue by PROMIS Setanaxib Doses Comb.
Comparison groups	Setanaxib 1200 mg/Day or 1600 mg/Day v Placebo
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3905
Method	Mixed Model Repeated Measures
Parameter estimate	LS mean difference vs placebo
Point estimate	-0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.496
upper limit	4.153

Secondary: Change in Fatigue at Week 24 Compared to Baseline, as Assessed by the PBC-40 Questionnaire (PBC 40) Fatigue Domain, Where Setanaxib Doses Are Combined

End point title	Change in Fatigue at Week 24 Compared to Baseline, as Assessed by the PBC-40 Questionnaire (PBC 40) Fatigue Domain, Where Setanaxib Doses Are Combined[14]

End point description:

PBC-40 fatigue domain includes 11 item questions, items scores range from 1 to 5. The individual item scores are summed to obtain a total domain score (Range for fatigue domain: 11 to 55), high scores represent high impact and low scores indicate low impact of PBC on the quality of life.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 24

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Combined doses and separate doses are reported as separate endpoints per study protocol.

End point values	Placebo	Setanaxib 1200 mg/Day or 1600 mg/Day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	47		
Units: units on a scale				
least squares mean (confidence interval 95%)	-1.84 (-5.176 to 1.492)	-1.64 (-4.096 to 0.826)		

Statistical analyses

Statistical analysis title	Change in Fatigue by PBC-40 Setanaxib Doses Comb.
Comparison groups	Setanaxib 1200 mg/Day or 1600 mg/Day v Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5393
Method	Mixed Model Repeated Measures
Parameter estimate	LS mean difference vs placebo
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.968
upper limit	4.381

Secondary: Change in Liver Stiffness at Week 24 Compared to Screening, Where Setanaxib Doses Are Combined

End point title	Change in Liver Stiffness at Week 24 Compared to Screening, Where Setanaxib Doses Are Combined[15]

End point description:

Change in liver stiffness at Week 24 compared to Screening, as assessed by transient elastography (FibroScan®)

End point type	Secondary

End point timeframe:

Screening (Day -28) and Week 24

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Combined doses and separate doses are reported as separate endpoints per study protocol.

End point values	Placebo	Setanaxib 1200 mg/Day or 1600 mg/Day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	49		
Units: ratio				
least squares mean (confidence interval 95%)	0.92 (0.809 to 1.056)	0.83 (0.750 to 0.921)		

Statistical analyses

Statistical analysis title	Change in Liver Stiffness Setanaxib Doses Combined
Comparison groups	Setanaxib 1200 mg/Day or 1600 mg/Day v Placebo
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1079
Method	Mixed Model Repeated Measures
Parameter estimate	Ratio of geometric LS mean vs placebo
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.759
upper limit	1.065

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Reporting of adverse events will begin when the patient has provided informed consent and will continue up to 30 days after the last IMP administration.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Setanaxib 1200 mg/Day
Reporting group description: -	
Reporting group title	Setanaxib 1600 mg/Day
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Setanaxib 1200 mg/Day	Setanaxib 1600 mg/Day	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 25 (16.00%)	2 / 25 (8.00%)	3 / 26 (11.54%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	0 / 26 (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
Vascular disorders			
Hypertensive urgency			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocarditis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Pancreatitis acute			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 26 (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			
Drug-induced liver injury			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 26 (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
Musculoskeletal and connective tissue disorders			
Oligoarthritis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 26 (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
Metabolism and nutrition disorders			
Folate deficiency			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 26 (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
Iron deficiency			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 26 (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

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

Non-serious adverse events	Setanaxib 1200 mg/Day	Setanaxib 1600 mg/Day	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 25 (72.00%)	19 / 25 (76.00%)	22 / 26 (84.62%)
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 25 (12.00%)	3 / 25 (12.00%)	3 / 26 (11.54%)
occurrences (all)	4	3	3
Asthenia			
subjects affected / exposed	2 / 25 (8.00%)	0 / 25 (0.00%)	0 / 26 (0.00%)
occurrences (all)	3	0	0
Reproductive system and breast disorders			
Cough			
subjects affected / exposed	0 / 25 (0.00%)	2 / 25 (8.00%)	0 / 26 (0.00%)
occurrences (all)	0	5	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 25 (0.00%)	2 / 25 (8.00%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 25 (0.00%)	2 / 25 (8.00%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 25 (0.00%)	2 / 25 (8.00%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 25 (0.00%)	2 / 25 (8.00%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 25 (0.00%)	2 / 25 (8.00%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
Nervous system disorders			
Headache			

subjects affected / exposed	3 / 25 (12.00%)	0 / 25 (0.00%)	5 / 26 (19.23%)
occurrences (all)	3	0	7
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	2
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	2
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 25 (0.00%)	2 / 25 (8.00%)	7 / 26 (26.92%)
occurrences (all)	0	2	8
Diarrhoea			
subjects affected / exposed	2 / 25 (8.00%)	2 / 25 (8.00%)	0 / 26 (0.00%)
occurrences (all)	2	2	0
Abdominal pain			
subjects affected / exposed	2 / 25 (8.00%)	0 / 25 (0.00%)	2 / 26 (7.69%)
occurrences (all)	2	0	2
Abdominal pain upper			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	3 / 26 (11.54%)
occurrences (all)	0	0	3
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	0 / 25 (0.00%)	2 / 25 (8.00%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	6 / 26 (23.08%)
occurrences (all)	0	0	8
Rash			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	2
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	2 / 25 (8.00%)	4 / 25 (16.00%)	3 / 26 (11.54%)
occurrences (all)	3	5	3
Back pain			
subjects affected / exposed	0 / 25 (0.00%)	2 / 25 (8.00%)	2 / 26 (7.69%)
occurrences (all)	0	2	2
Pain in extremity			
subjects affected / exposed	0 / 25 (0.00%)	2 / 25 (8.00%)	0 / 26 (0.00%)
occurrences (all)	0	5	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 25 (12.00%)	4 / 25 (16.00%)	0 / 26 (0.00%)
occurrences (all)	4	8	0
COVID-19			
subjects affected / exposed	3 / 25 (12.00%)	3 / 25 (12.00%)	0 / 26 (0.00%)
occurrences (all)	3	3	0
Influenza			
subjects affected / exposed	0 / 25 (0.00%)	2 / 25 (8.00%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 25 (0.00%)	2 / 25 (8.00%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
Urinary tract infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	2
Gastroenteritis viral			
subjects affected / exposed	0 / 25 (0.00%)	2 / 25 (8.00%)	0 / 26 (0.00%)
occurrences (all)	0	2	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 May 2022	The protocol was amended to reflect the following key changes, which were incorporated in the protocol and protocol summary where applicable: 1. Based on FDA requests, changes were made to the PRO measures used in the study and Key Secondary Endpoints. 2. The 2 errors that had been identified and described in the protocol clarification letter dated 05 July 2021 were corrected (IMP was not to be dispensed at the Week 104/Year 2 Visit, and for PBC 40, addition that 3 additional questions related to general health and well-being were part of the questionnaire). 3. Changes implemented in the local UK, Spanish, Austrian, and German revised protocols were incorporated in the global amendment. This includes an added on-site visit at Week 4. 4. Language on product complaint reporting was added. 5. Changes to the Concomitant Medication and Procedures Section 6.7 based on a request from the Belgian Regulatory Authority. In addition, the following non-substantial revisions and corrections have been incorporated in the protocol and protocol summary where applicable: 1. Genkyotex Suisse SA has been renamed Calliditas Therapeutics Suisse SA effective 01 April 2022. 2. Clarification of Inclusion Criterion #10b 3. The exclusion criteria numbering has been revised to ensure alignment and consistency across all versions of the protocol. 4. Background Section 1.1 includes minor revisions to align with the Investigator Brochure, Edition 12.0.
11 April 2023	The protocol has been amended to reflect the following key changes, which have been incorporated in the protocol and protocol summary where applicable: 1. If futility is not met for the setanaxib 1200 mg/day and 1600 mg/day doses, the Independent Data Monitoring Committee (IDMC) will select one dose for Stage 2. Ongoing patients who are receiving the selected dose will continue the study at the same dose. Ongoing patients who are receiving a dose that is discontinued will have their dose escalated/de-escalated to the selected dose. Patients enrolled after the interim analysis will be randomized to setanaxib (dose selected by the IDMC), or placebo, according to a 1:1 randomization ratio, up to full enrollment. 2. An analysis of the proportion of patients with alkaline phosphatase (ALP) reduction of ≥70% reduction from Baseline at Week 52 and changes in markers of cholestasis as assessed by proportion of patients at Week 52 with ALP reduction to <1.5×upper limit of normal (ULN) and total bilirubin ≤1×ULN and with a ≥40% ALP reduction from Baseline have been added following recommendations from the FDA and the European Medicines Agency, respectively. 3. Inclusion criterion 5 was updated to allow patients with liver stiffness of ≥8.0 kPa (previously ≥8.8 kPa). 4. The exploratory endpoint of changes in markers of cholestasis has been upgraded to secondary endpoint (as abovementioned). 5. The list of prohibited medications was updated with regards to corticosteroid use and removal of biologics.

26 October 2023	The study design was revised to a Phase 2b study with the following key changes: 1a. Revision of primary and secondary objectives, ie, the decrease in ALP from Baseline at 24 weeks as primary objective and no further selection of a key secondary parameter. b. Regarding the new primary endpoint: bi. A new sample size calculation was performed that resulted in 60 to 70 patients instead of 318, and a reduced number of sites (80 to 130). bii. The statistical methods planned to be applied were revised. c. Reduction of the Double-blind Treatment Period from 1 year to 24 weeks. d. The rationale for a 52-week Extension Phase Treatment Period was no longer applicable; therefore, this period as well as the 12-week Follow up Period were removed. e. With the reduction of the Double-blind Treatment Period to 24 weeks, the optional liver biopsy at Week 52 was removed; it was not expected to find effects at an earlier time point. f. The rationale for an interim analysis, ie, the assessment of futility and dose selection, was no longer applicable; therefore, the interim analysis was removed. The study design was no longer adaptive. g. Corresponding to changes to the overall study design, the statistical methods planned to be applied were revised, including the definition of the FAS, handling of missing data values, the plans for sensitivity and supplementary analyses. 2. Exclusion criterion 18 was removed. 3. The criterion for premature discontinuation of the IMP was amended for patients with a severe cardiac condition or QT prolongation or an increase in QTc greater than 60 milliseconds from Baseline. Patients who were following the previous protocol schedule (protocol version 4) and were already beyond Week 24 were to permanently discontinue IMP as soon as possible and have an End-of-Treatment Visit 30 days after their last dose.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported