Clinical trial results:
A randomized, double-blind, dose-ranging, placebo-controlled, Phase 2a evaluation of the safety, tolerability, and pharmacokinetics of PLN-74809 in participants with primary sclerosing cholangitis (PSC) and suspected liver fibrosis (INTEGRIS-PSC)

Summary

EudraCT number	2020-001428-33
Trial protocol	GB AT DE BE FR NL
Global end of trial date	18 March 2024

Results information

Result version number	v1 (current)
This version publication date	06 April 2025
First version publication date	06 April 2025

Trial information

Trial identification

Sponsor protocol code	PLN-74809-PSC-203

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04480840
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pliant Therapeutics Inc.
Sponsor organisation address	331 Oyster Point Blvd, South San Francisco, United States, CA 94080
Public contact	Monica Sandberg, Pliant Therapeutics Inc., +1 650481 6770, Msandberg@pliantrx.com
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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	21 November 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 March 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and tolerability of PLN-74809 following daily administration for up to 12 weeks in participants with PSC in part 1 and part 2 and part 3 for at least 24 weeks and up to 48 weeks.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.
All study subjects were required to read and sign an Informed Consent Form.

Background therapy:

Participants who were receiving the following medications were allowed: treatment with UDCA, therapy is at a dose of < 25 mg/kg/day, has been stable for at least 3 months before screening concomitant medications for the treatment of IBD, therapy was stable from screening and expected to remain stable for the duration of the study.

Evidence for comparator: -

Actual start date of recruitment	19 August 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 44
Country: Number of subjects enrolled	United States: 43
Country: Number of subjects enrolled	Australia: 8
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 3
Worldwide total number of subjects	121
EEA total number of subjects	16

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)	110
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were screened at 52 centers in 9 countries. This study was divided into 3 parts, each study part included an up to 42-day Screening period, followed by a treatment period of either 12 weeks (Parts 1 and 2) or at least 24 weeks and up to 48 weeks (Part 3), and finally a 4-week post-treatment follow-up period.

Pre-assignment

Screening details:

201 participants underwent Screening: 102 participants failed screening and 28 participants were rescreened, of whom 18 were randomized. In total, 112 screen failures including both participants who were counted twice due to re-screening and those who were an initial screening failure but successfully

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1: Bexotegrast 40 mg

Arm description:

Part 1: 42-day Screening period, followed by a treatment period of 12 weeks (Bexotegrast 40 mg) and finally 4-week post-treatment follow-up period.
Participants took either Bexotegrast 40mg or a matching placebo

Arm type	Experimental
Investigational medicinal product name	PLN-74809
Investigational medicinal product code	
Other name	Bexotegrast
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Study drug (Bexotegrast 40 mg) will be taken once daily at approximately 24-hour intervals.
Participants will take the study drug on an empty stomach (no food for 2 hours before or 2 hours after dosing) and will drink approximately 240 mL (~1 cup) of water after swallowing the study drug

Arm title	Part 2: Bexotegrast 80 mg

Arm description:

Part 2: 42-day Screening period, followed by a treatment period of 12 weeks (Bexotegrast 80 mg) and finally 4-week post-treatment follow-up period
Participants took either Bexotegrast 80mg or a matching placebo

Arm type	Experimental
Investigational medicinal product name	PLN-74809
Investigational medicinal product code	
Other name	Bexotegrast
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Study drug (Bexotegrast 80 mg) will be taken once daily at approximately 24-hour intervals.
Participants will take the study drug on an empty stomach (no food for 2 hours before or 2 hours after dosing) and will drink approximately 240 mL (~1 cup) of water after swallowing the study drug

Arm title	Part 2: Bexotegrast 160 mg

Arm description:

Part 2: 42-day Screening period, followed by a treatment period of 12 weeks (Bexotegrast 160 mg) and finally 4-week post-treatment follow-up period
Participants took either Bexotegrast 160mg or a matching placebo

Arm type	Experimental
Investigational medicinal product name	PLN-74809
Investigational medicinal product code	
Other name	Bexotegrast
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Study drug (Bexotegrast 160 mg) will be taken once daily at approximately 24-hour intervals. Participants will take the study drug on an empty stomach (no food for 2 hours before or 2 hours after dosing) and will drink approximately 240 mL (~1 cup) of water after swallowing the study drug

Arm title	Part 3: Bexotegrast 320 mg

Arm description:

Part 3: 42-day Screening period, followed by a treatment period for at least 24 weeks and up to 48 weeks (Bexotegrast 320 mg) and finally 4-week post-treatment follow-up period. ongoing safety and liver assessments continued until the last participant reached 24 weeks of the study; therefore, safety and laboratory assessments could extend to up to 48 weeks.
4 participants in Part 3 previously completed participation in either Part 1 or Part 2 with a minimum of 6 months between completion of the earlier part and participation in Part 3

Arm type	Experimental
Investigational medicinal product name	PLN-74809
Investigational medicinal product code	
Other name	Bexotegrast
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Study drug (Bexotegrast 320 mg) will be taken once daily at approximately 24-hour intervals. Participants will take the study drug on an empty stomach (no food for 2 hours before or 2 hours after dosing) and will drink approximately 240 mL (~1 cup) of water after swallowing the study drug

Arm title	Placebo

Arm description:

Matching placebo tablets

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

Dosage and administration details:

Study drug (placebo) will be taken once daily at approximately 24-hour intervals. Participants will take the study drug on an empty stomach (no food for 2 hours before or 2 hours after dosing) and will drink approximately 240 mL (~1 cup) of water after swallowing the study drug

Number of subjects in period 1	Part 1: Bexotegrast 40 mg	Part 2: Bexotegrast 80 mg	Part 2: Bexotegrast 160 mg
Started	24	20	20
Completed	22	19	19
Not completed	2	1	1
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	1	1	1
Other	-	-	-
Protocol deviation	1	-	-

Number of subjects in period 1	Part 3: Bexotegrast 320 mg	Placebo
Started	27	30
Completed	23	28
Not completed	4	2
Consent withdrawn by subject	2	-
Adverse event, non-fatal	1	2
Other	1	-
Protocol deviation	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Part 1: Bexotegrast 40 mg
Reporting group description:	
Part 1: 42-day Screening period, followed by a treatment period of 12 weeks (Bexotegrast 40 mg) and finally 4-week post-treatment follow-up period. Participants took either Bexotegrast 40mg or a matching placebo	
Reporting group title	Part 2: Bexotegrast 80 mg
Reporting group description:	
Part 2: 42-day Screening period, followed by a treatment period of 12 weeks (Bexotegrast 80 mg) and finally 4-week post-treatment follow-up period Participants took either Bexotegrast 80mg or a matching placebo	
Reporting group title	Part 2: Bexotegrast 160 mg
Reporting group description:	
Part 2: 42-day Screening period, followed by a treatment period of 12 weeks (Bexotegrast 160 mg) and finally 4-week post-treatment follow-up period Participants took either Bexotegrast 160mg or a matching placebo	
Reporting group title	Part 3: Bexotegrast 320 mg
Reporting group description:	
Part 3: 42-day Screening period, followed by a treatment period for at least 24 weeks and up to 48 weeks (Bexotegrast 320 mg) and finally 4-week post-treatment follow-up period. ongoing safety and liver assessments continued until the last participant reached 24 weeks of the study; therefore, safety and laboratory assessments could extend to up to 48 weeks. 4 participants in Part 3 previously completed participation in either Part 1 or Part 2 with a minimum of 6 months between completion of the earlier part and participation in Part 3	
Reporting group title	Placebo
Reporting group description:	
Matching placebo tablets	

Reporting group values	Part 1: Bexotegrast 40 mg	Part 2: Bexotegrast 80 mg	Part 2: Bexotegrast 160 mg
Number of subjects	24	20	20
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	46.9	40.5	45.1
standard deviation	± 15.06	± 15.32	± 12.65

Gender categorical Units: Subjects			
Female	7	4	6
Male	17	16	14
Fertility Status Units: Subjects			
Childbearing Potential	1	3	3
Post-Menopausal	3	1	3
Surgically Sterile	3	0	0
Missing	0	0	0
Not Female	17	16	14
Participant taking UDCA Units: Subjects			
Yes	14	15	13
No	10	5	7
Ethnicity Units: Subjects			
Hispanic or Latino	1	1	2
Not Hispanic or Latino	23	18	18
Not Reported/ Unknown	0	1	0
Race Units: Subjects			
White	20	16	18
Black or African American	2	2	1
Asian	2	1	1
American Indian or Alaska Native	0	0	0
Nativ Hawaiian or Other Pacific Islander	0	0	0
Not Reported/Unknown	0	0	0
Other	0	1	0
Duration of UDCA Use Units: Years			
arithmetic mean	8.27	7.75	4.60
standard deviation	± 4.551	± 10.837	± 4.034
Height at Screening Units: cm			
arithmetic mean	175.37	175.95	173.69
standard deviation	± 9.509	± 9.155	± 9.876
Weight at Screening Units: kg			
arithmetic mean	86.64	81.77	80.59
standard deviation	± 15.718	± 14.098	± 16.774
BMI at Screening Units: kg/m2			
arithmetic mean	28.21	26.45	26.82
standard deviation	± 5.167	± 4.506	± 5.950
Duration Since Diagnosis Units: Years			
arithmetic mean	11.1	8.3	7.8
standard deviation	± 8.15	± 7.97	± 6.78

Reporting group values	Part 3: Bexotegrast	Placebo	Total

			320 mg
Number of subjects	27	30	121
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	47.1	45.2	
standard deviation	± 14.47	± 11.65	-
Gender categorical Units: Subjects			
Female	14	6	37
Male	13	24	84
Fertility Status Units: Subjects			
Childbearing Potential	1	3	11
Post-Menopausal	11	2	20
Surgically Sterile	1	1	5
Missing	1	0	1
Not Female	13	24	84
Participant taking UDCA Units: Subjects			
Yes	18	19	79
No	9	11	42
Ethnicity Units: Subjects			
Hispanic or Latino	0	3	7
Not Hispanic or Latino	25	26	110
Not Reported/ Unknown	2	1	4
Race Units: Subjects			
White	26	25	105
Black or African American	0	2	7
Asian	1	1	6
American Indian or Alaska Native	0	0	0
Nativ Hawaiian or Other Pacific Islander	0	0	0
Not Reported/Unknown	0	2	2
Other	0	0	1
Duration of UDCA Use Units: Years			
arithmetic mean	7.64	5.17	

standard deviation	± 6.325	± 6.241	-
Height at Screening			
Units: cm			
arithmetic mean	173.17	176.71	
standard deviation	± 9.655	± 9.127	-
Weight at Screening			
Units: kg			
arithmetic mean	74.09	82.94	
standard deviation	± 13.375	± 15.217	-
BMI at Screening			
Units: kg/m2			
arithmetic mean	24.60	26.44	
standard deviation	± 3.069	± 3.562	-
Duration Since Diagnosis			
Units: Years			
arithmetic mean	9.4	9.0	
standard deviation	± 11.20	± 7.34	-

Subject analysis sets

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population is defined as all randomized participants who receive at least 1 dose of study drug.

Subject analysis set title	PD Analysis Set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PD analysis population is defined as all participants in the safety population who have an evaluable baseline and at least 1 evaluable postbaseline PD measurement.

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

Subject analysis set description:

The PK concentration population is defined as all participants in the safety population who have any valid PLN-74809 concentration data not including BLQ values.

Reporting group values	Safety Population	PD Analysis Set	PK Analysis Set
Number of subjects	121	121	121
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			

Age continuous Units: years			
arithmetic mean	44.9	44.9	44.9
standard deviation	± 13.91	± 13.91	± 13.91
Gender categorical Units: Subjects			
Female	37	37	37
Male	84	84	84
Fertility Status Units: Subjects			
Childbearing Potential	11	11	11
Post-Menopausal	20	20	20
Surgically Sterile	5	5	5
Missing	1	1	1
Not Female	84	84	84
Participant taking UDCA Units: Subjects			
Yes	79	79	79
No	42	42	42
Ethnicity Units: Subjects			
Hispanic or Latino	7	79	79
Not Hispanic or Latino	110	110	110
Not Reported/ Unknown	4	4	4
Race Units: Subjects			
White	105	105	105
Black or African American	7	7	7
Asian	6	6	6
American Indian or Alaska Native	0	0	0
Nativ Hawaiian or Other Pacific Islander	0	0	0
Not Reported/Unknown	2	2	2
Other	1	1	1
Duration of UDCA Use Units: Years			
arithmetic mean	6.70	6.70	6.7
standard deviation	± 6.886	± 6.886	± 6.886
Height at Screening Units: cm			
arithmetic mean	175.05	175.05	175.05
standard deviation	± 9.434	± 9.434	± 9.434
Weight at Screening Units: kg			
arithmetic mean	81.36	81.36	81.36
standard deviation	± 15.484	± 15.484	± 15.484
BMI at Screening Units: kg/m2			
arithmetic mean	26.52	26.52	26.52
standard deviation	± 4.566	± 4.566	± 4.566
Duration Since Diagnosis Units: Years			

arithmetic mean standard deviation	9.0 ± 8.42	9.0 ± 8.42	9.0 ± 8.42

End points

End points reporting groups

Reporting group title	Part 1: Bexotegrast 40 mg

Reporting group description:

Part 1: 42-day Screening period, followed by a treatment period of 12 weeks (Bexotegrast 40 mg) and finally 4-week post-treatment follow-up period.
Participants took either Bexotegrast 40mg or a matching placebo

Reporting group title	Part 2: Bexotegrast 80 mg

Reporting group description:

Part 2: 42-day Screening period, followed by a treatment period of 12 weeks (Bexotegrast 80 mg) and finally 4-week post-treatment follow-up period
Participants took either Bexotegrast 80mg or a matching placebo

Reporting group title	Part 2: Bexotegrast 160 mg

Reporting group description:

Part 2: 42-day Screening period, followed by a treatment period of 12 weeks (Bexotegrast 160 mg) and finally 4-week post-treatment follow-up period
Participants took either Bexotegrast 160mg or a matching placebo

Reporting group title	Part 3: Bexotegrast 320 mg

Reporting group description:

Part 3: 42-day Screening period, followed by a treatment period for at least 24 weeks and up to 48 weeks (Bexotegrast 320 mg) and finally 4-week post-treatment follow-up period. ongoing safety and liver assessments continued until the last participant reached 24 weeks of the study; therefore, safety and laboratory assessments could extend to up to 48 weeks.
4 participants in Part 3 previously completed participation in either Part 1 or Part 2 with a minimum of 6 months between completion of the earlier part and participation in Part 3

Reporting group title	Placebo

Reporting group description:

Matching placebo tablets

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population is defined as all randomized participants who receive at least 1 dose of study drug.

Subject analysis set title	PD Analysis Set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The PD analysis population is defined as all participants in the safety population who have an evaluable baseline and at least 1 evaluable postbaseline PD measurement.

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

Subject analysis set description:

The PK concentration population is defined as all participants in the safety population who have any valid PLN-74809 concentration data not including BLQ values.

Primary: Number of Participants with Treatment-Emergent Adverse Events

End point title	Number of Participants with Treatment-Emergent Adverse Events[1]

End point description:

The primary endpoint is the nature and proportion of treatment-emergent adverse events (TEAEs) between PLN-74809 and placebo groups (descriptive)

End point type	Primary

End point timeframe:

Up to 40 Weeks

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: There is no statistical analysis planned for the number of TEAEs

End point values	Part 1: Bexotegrast 40 mg	Part 2: Bexotegrast 80 mg	Part 2: Bexotegrast 160 mg	Part 3: Bexotegrast 320 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	20	20	27
Units: Subjects	10	16	15	23

End point values	Placebo	Safety Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	30	121		
Units: Subjects	21	64		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Serious Treatment-Emergent Adverse Events

End point title	Number of Participants with Serious Treatment-Emergent Adverse Events[2]

End point description:

End point type	Primary

End point timeframe:

Up to 40 Weeks

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There is no statistical analysis planned for the number of TEAEs

End point values	Part 1: Bexotegrast 40 mg	Part 2: Bexotegrast 80 mg	Part 2: Bexotegrast 160 mg	Part 3: Bexotegrast 320 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	20	20	27
Units: Subjects	1	1	0	1

End point values	Placebo	Safety Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	30	121		
Units: Subjects	1	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration at Week 12, 2 Hour Post Dose

End point title	Plasma Concentration at Week 12, 2 Hour Post Dose

End point description:

End point type	Secondary

End point timeframe:

Up to 12 weeks

End point values	Part 1: Bexotegrast 40 mg	Part 2: Bexotegrast 80 mg	Part 2: Bexotegrast 160 mg	Part 3: Bexotegrast 320 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	18	19	24
Units: ng/mL				
arithmetic mean (standard deviation)	638.71 (± 378.193)	843.06 (± 474.312)	2035.95 (± 1020.567)	3667.50 (± 1598.067)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: ng/mL				
arithmetic mean (standard deviation)	0 (± 0)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Plasma Concentration at Week 24, 2 Hour Post Dose

End point title	Plasma Concentration at Week 24, 2 Hour Post Dose[3]

End point description:

End point type	Other pre-specified

End point timeframe:

Up to 24 weeks

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: Only Part 3 and Placebo continued to Week 24

End point values	Part 3: Bexotegrast 320 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	9		
Units: ng/mL				
arithmetic mean (standard deviation)	3583.64 (± 1642.404)	0 (± 0)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percent Change from Baseline PRO-C3 Liver Fibrosis Biomarker at Week 12

End point title	Percent Change from Baseline PRO-C3 Liver Fibrosis Biomarker at Week 12

End point description:

End point type	Other pre-specified

End point timeframe:

Up to 12 weeks

End point values	Part 1: Bexotegrast 40 mg	Part 2: Bexotegrast 80 mg	Part 2: Bexotegrast 160 mg	Part 3: Bexotegrast 320 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	17	18	25
Units: ng/mL				
arithmetic mean (standard deviation)	-3.78 (± 20.471)	7.12 (± 20.328)	5.20 (± 30.899)	2.70 (± 36.130)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: ng/mL				
arithmetic mean (standard deviation)	22.35 (± 53.183)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percent Change from Baseline PRO-C3 Liver Fibrosis Biomarker at Week 24

End point title	Percent Change from Baseline PRO-C3 Liver Fibrosis Biomarker at Week 24[4]

End point description:

End point type	Other pre-specified

End point timeframe:

Up to 24 weeks

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: Only Part 3 and Placebo continued to Week 24

End point values	Part 3: Bexotegrast 320 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	9		
Units: ng/mL				
arithmetic mean (standard deviation)	-12.74 (± 26.539)	-1.38 (± 36.859)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from Baseline Enhanced Liver Fibrosis (ELF) Total Score at Week 12

End point title	Change from Baseline Enhanced Liver Fibrosis (ELF) Total Score at Week 12

End point description:

End point type	Other pre-specified

End point timeframe:

Up to 12 weeks

End point values	Part 1: Bexotegrast 40 mg	Part 2: Bexotegrast 80 mg	Part 2: Bexotegrast 160 mg	Part 3: Bexotegrast 320 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	21	19	19	26
Units: unitless				
arithmetic mean (standard deviation)	0.16 (± 0.58)	0.19 (± 0.51)	0.09 (± 0.55)	0.19 (± 0.59)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: unitless				
arithmetic mean (standard deviation)	0.42 (± 0.745)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from Baseline Enhanced Liver Fibrosis (ELF) Total Score at Week 24

End point title	Change from Baseline Enhanced Liver Fibrosis (ELF) Total Score at Week 24[5]

End point description:

End point type	Other pre-specified

End point timeframe:

Up to 24 weeks

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: Only Part 3 and Placebo continued to Week 24

End point values	Part 3: Bexotegrast 320 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	9		
Units: unitless				
arithmetic mean (standard deviation)	0.19 (± 7.64)	0.14 (± 0.58)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from Baseline Serum Alkaline Phosphatase (ALP) at Week 12

End point title	Change from Baseline Serum Alkaline Phosphatase (ALP) at Week 12

End point description:

End point type	Other pre-specified

End point timeframe:

Up to 12 weeks

End point values	Part 1: Bexotegrast 40 mg	Part 2: Bexotegrast 80 mg	Part 2: Bexotegrast 160 mg	Part 3: Bexotegrast 320 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	19	19	25
Units: U/L				
arithmetic mean (standard deviation)	7.5 (± 83.20)	4.8 (± 33.56)	-7.5 (± 34.63)	1.7 (± 44.81)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: U/L				
arithmetic mean (standard deviation)	40.2 (± 130.94)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from Baseline Alkaline Phosphatase (ALP) at Week 24

End point title	Change from Baseline Alkaline Phosphatase (ALP) at Week 24[6]

End point description:

End point type	Other pre-specified

End point timeframe:

Up to 24 weeks

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: Only Part 3 and Placebo continued to Week 24

End point values	Part 3: Bexotegrast 320 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	9		
Units: U/L				
arithmetic mean (standard deviation)	-26.1 (± 66.55)	34.4 (± 56.57)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 40 weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups	
Reporting group title	Part 1: Bexotegrast 40 mg
Reporting group description:	
The Safety analysis population includes all randomized participants who receive at least one dose of study drug.	
Reporting group title	Part 2: Bexotegrast 80 mg
Reporting group description: -	
Reporting group title	Part 2: Bexotegrast 160 mg
Reporting group description: -	
Reporting group title	Part 3: Bexotegrast 320 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Part 1: Bexotegrast 40 mg	Part 2: Bexotegrast 80 mg	Part 2: Bexotegrast 160 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 24 (4.17%)	1 / 20 (5.00%)	0 / 20 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 24 (4.17%)	0 / 20 (0.00%)	0 / 20 (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			
Cholangitis			
subjects affected / exposed	0 / 24 (0.00%)	1 / 20 (5.00%)	0 / 20 (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
Cholecystitis			

subjects affected / exposed	1 / 24 (4.17%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Enterobacter bacteraemia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part 3: Bexotegrast 320 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 27 (3.70%)	1 / 30 (3.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 27 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 27 (3.70%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Enterobacter bacteraemia			
subjects affected / exposed	1 / 27 (3.70%)	0 / 30 (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	Part 1: Bexotegrast 40 mg	Part 2: Bexotegrast 80 mg	Part 2: Bexotegrast 160 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 24 (41.67%)	16 / 20 (80.00%)	15 / 20 (75.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 24 (0.00%)	0 / 20 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 24 (0.00%)	0 / 20 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Headache			
subjects affected / exposed	1 / 24 (4.17%)	2 / 20 (10.00%)	3 / 20 (15.00%)
occurrences (all)	1	2	3
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 24 (12.50%)	2 / 20 (10.00%)	4 / 20 (20.00%)
occurrences (all)	3	2	5
Pyrexia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 24 (4.17%)	2 / 20 (10.00%)	0 / 20 (0.00%)
occurrences (all)	1	2	0
Abdominal pain upper			
subjects affected / exposed	2 / 24 (8.33%)	2 / 20 (10.00%)	0 / 20 (0.00%)
occurrences (all)	2	2	0
Colitis ulcerative			
subjects affected / exposed	0 / 24 (0.00%)	1 / 20 (5.00%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	1 / 24 (4.17%)	2 / 20 (10.00%)	1 / 20 (5.00%)
occurrences (all)	1	2	1
Diarrhoea			

subjects affected / exposed	2 / 24 (8.33%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	2	0	0
Dyspepsia			
subjects affected / exposed	0 / 24 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Frequent bowel movements			
subjects affected / exposed	0 / 24 (0.00%)	3 / 20 (15.00%)	0 / 20 (0.00%)
occurrences (all)	0	3	0
Nausea			
subjects affected / exposed	1 / 24 (4.17%)	2 / 20 (10.00%)	3 / 20 (15.00%)
occurrences (all)	1	2	3
Vomiting			
subjects affected / exposed	1 / 24 (4.17%)	2 / 20 (10.00%)	0 / 20 (0.00%)
occurrences (all)	1	2	0
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 24 (0.00%)	1 / 20 (5.00%)	1 / 20 (5.00%)
occurrences (all)	0	2	1
Ocular Icterus			
subjects affected / exposed	0 / 24 (0.00%)	0 / 20 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
COVID-19			
subjects affected / exposed	2 / 24 (8.33%)	1 / 20 (5.00%)	0 / 20 (0.00%)
occurrences (all)	2	1	0
Nasopharyngitis			
subjects affected / exposed	0 / 24 (0.00%)	2 / 20 (10.00%)	0 / 20 (0.00%)
occurrences (all)	0	3	0

Non-serious adverse events	Part 3: Bexotegrast 320 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 27 (85.19%)	21 / 30 (70.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 27 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			

Dizziness			
subjects affected / exposed	0 / 27 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	3 / 27 (11.11%)	4 / 30 (13.33%)	
occurrences (all)	3	5	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 27 (11.11%)	5 / 30 (16.67%)	
occurrences (all)	3	6	
Pyrexia			
subjects affected / exposed	0 / 27 (0.00%)	3 / 30 (10.00%)	
occurrences (all)	0	4	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 27 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Abdominal pain upper			
subjects affected / exposed	2 / 27 (7.41%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
Colitis ulcerative			
subjects affected / exposed	3 / 27 (11.11%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
Constipation			
subjects affected / exposed	0 / 27 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	4 / 27 (14.81%)	0 / 30 (0.00%)	
occurrences (all)	4	0	
Dyspepsia			
subjects affected / exposed	0 / 27 (0.00%)	3 / 30 (10.00%)	
occurrences (all)	0	3	
Frequent bowel movements			
subjects affected / exposed	0 / 27 (0.00%)	3 / 30 (10.00%)	
occurrences (all)	0	4	
Nausea			

subjects affected / exposed	1 / 27 (3.70%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	2 / 27 (7.41%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 27 (3.70%)	4 / 30 (13.33%)	
occurrences (all)	3	6	
Ocular Icterus			
subjects affected / exposed	0 / 27 (0.00%)	3 / 30 (10.00%)	
occurrences (all)	0	3	
Infections and infestations			
COVID-19			
subjects affected / exposed	5 / 27 (18.52%)	4 / 30 (13.33%)	
occurrences (all)	5	4	
Nasopharyngitis			
subjects affected / exposed	5 / 27 (18.52%)	1 / 30 (3.33%)	
occurrences (all)	6	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 April 2020	Protocol amendment 1 Version 1.0 US (Sequential dosing): Removed Part 2
06 May 2020	Protocol amendment 1 Version 1.1 (Parallel dosing): Removed Part 2
14 December 2020	Protocol amendment 2 Version 1.0 (Sequential dosing): Corrected IND number. Investigational Plan: clarifications. Revised Inclusion Criteria: 2. Revised serum ALP concentration. Clarified and specified the criteria by which Investigators can determine suspected hepatic fibrosis. Revised platelet count. Revised exclusion criteria: Clarified worsening of liver disease. Description of Treatments: Added: Description and rationale for study doses and placebo (40, 80, and 160 mg) and study design for Part 2 Clarification that Part 2 will be randomly assigned (3:1) in parallel treatment cohorts. Selection and Timing of Dose for Each Participant: added language to provide guidance in the even a participant misses a dose of study drug. Allowed Medications: Revised prednisone doses. Disallowed Medications: Added: New contraception language for male and female participants of childbearing potential. Study Procedures: Retesting of a screening laboratory test(s) and/or ultrasound-based transient elastography (FibroScan®) may be permitted once. Liver Imaging (optional): Clarification. Electrocardiograms: Added language regarding triplicate ECG. Definition of SAEs: Added clarification as to which events would not be defined as SAEs. Early Discontinuation of Study or Individual Participants clarification. Retention for the study data for 25 years if per local requirements. Schedule of Assessments, appendix 1: Added or revised assessments to align with revised study procedures
06 January 2021	Protocol amendment 2 Version 1.1 (Parallel dosing): Corrected IND number. Investigational Plan: clarifications. Revised Inclusion Criteria: 2. Revised serum ALP concentration. Clarified and specified the criteria by which Investigators can determine suspected hepatic fibrosis. Revised platelet count. Revised exclusion criteria: Clarified worsening of liver disease. Description of Treatments: Added: Description and rationale for study doses and placebo (40, 80, and 160 mg) and study design for Part 2 Clarification that Part 2 will be randomly assigned (3:1) in parallel treatment cohorts. Selection and Timing of Dose for Each Participant: added language to provide guidance in the even a participant misses a dose of study drug. Allowed Medications: Revised prednisone doses. Disallowed Medications: Added: New contraception language for male and female participants of childbearing potential. Study Procedures: Retesting of a screening laboratory test(s) and/or ultrasound-based transient elastography (FibroScan®) may be permitted once. Liver Imaging (optional): Clarification. Electrocardiograms: Added language regarding triplicate ECG. Definition of SAEs: Added clarification as to which events would not be defined as SAEs. Early Discontinuation of Study or Individual Participants clarification. Retention for the study data for 25 years if per local requirements. Schedule of Assessments, appendix 1: Added or revised assessments to align with revised study procedures

10 January 2022	Protocol amendment 3 Version 1.0 (Sequential dosing): Added background information on bexotegrast Updated to include new information for ongoing and completed studies. Investigational Plan: Added: Description and rationale for 320 mg QD dose for Part 3 following DSMB to evaluate the current 80 and 160 mg dose from Part 2. Data are reviewed by the DSMB; removed option for review by Competent Authorities (if applicable). Revised Inclusion Criterion 7. Revised Exclusion Criterion 18. Revised Exclusion Criterion 21. New formulation (phosphate salt formulation of bexotegrast) to be used in Part 3 (supplied as 80-mg immediate-release tablets). Revised storage conditions. Blinding: Added clarification that contacting the Sponsor's Study Director before unblinding. Added additional data from medication-medication interaction studies between bexotegrast and fluconazole and digoxin. Revised definition of postmenopausal state. Removed option for use of liver MRI within 3 months of Screening as an alternative to baseline MRI. Clarified that targeted physical examination will be performed based on prior findings in the general exam. List of Laboratory tests: Added prothrombin time (coagulation) and CA-19-9 (screening test). Clarified that pharmacogenomics sampling is optional. Causal Relationship of an Adverse Event: Corrected to Yes (related). Definition of SAEs: Clarified timing of pregnancy reporting. Added language to provide direction as to how AEs and serious adverse events are to be reported. Revision of process for reporting SAEs from utilizing EDC to pharmacovigilance vendor (CTI) Interim Analysis: Updated Section to include description of additional interim analyses. Appendix 2 Schedule of Assessments: Part 3: Added assessments and visits for Part 3.
11 January 2022	Protocol amendment 3 Version 1.1 (Parallel dosing): Added background information on bexotegrast Updated to include new information for ongoing and completed studies. Investigational Plan: Added: Description and rationale for 320 mg QD dose for Part 3 following DSMB to evaluate the current 80 and 160 mg dose from Part 2. Data are reviewed by the DSMB; removed option for review by Competent Authorities (if applicable). Revised Inclusion Criterion 7. Revised Exclusion Criterion 18. Revised Exclusion Criterion 21. New formulation (phosphate salt formulation of bexotegrast) to be used in Part 3 (supplied as 80-mg immediate-release tablets). Revised storage conditions. Blinding: Added clarification that contacting the Sponsor's Study Director before unblinding. Added additional data from medication-medication interaction studies between bexotegrast and fluconazole and digoxin. Revised definition of postmenopausal state. Removed option for use of liver MRI within 3 months of Screening as an alternative to baseline MRI. Clarified that targeted physical examination will be performed based on prior findings in the general exam. List of Laboratory tests: Added prothrombin time (coagulation) and CA-19-9 (screening test). Clarified that pharmacogenomics sampling is optional. Causal Relationship of an Adverse Event: Corrected to Yes (related). Definition of SAEs: Clarified timing of pregnancy reporting. Added language to provide direction as to how AEs and serious adverse events are to be reported. Revision of process for reporting SAEs from utilizing EDC to pharmacovigilance vendor (CTI) Interim Analysis: Updated Section to include description of additional interim analyses. Appendix 2 Schedule of Assessments: Part 3: Added assessments and visits for Part 3.
01 November 2022	Protocol amendment 4 Version 1.1 (Parallel dosing): Changed Sponsor Study Director from Greg Cosgrove to Richard Pencek. Revised Inclusion Criterion 9. Revised Inclusion Criterion 10. Revised Inclusion Criterion 3. Revised Exclusion Criterion 11. Revised Exclusion Criterion 28. Revised last bullet to "Treatment with a disallowed medication, other investigational drug within 5 half-lives or 30 days before Screening, whichever time is longer, or the use of an investigational device within 30 days before Screening is prohibited." Revised first sentence to "Prior use of an investigational drug within 5 half-lives or 30 days before Screening, whichever time is longer, or the use of an investigational device within 30 days before Screening is prohibited." Moved examples of contraceptive methods with a failure rate of <1% per year under new subheading "Highly Effective Methods of Birth Control." Revised the time between Visits 1 and 2 to be ≥2 weeks. Clarified that a plasma PK sample is not required at the EoS visit. Clarified that a plasma PK sample is not required at the EoS visit. Changes implemented for non-US sites: - Added Exclusion Criterion 29 to exclude participants who participated in an earlier part of the current study (ie, Part 1 or 2) within 6 months of dosing for a subsequent part (ie, Part 2 or 3); - Revised Exclusion Criterion 7.

07 November 2022	Protocol amendment 4 Version 1.0 (Sequential dosing): Changed Sponsor Study Director from Greg Cosgrove to Richard Pencek. Revised Inclusion Criterion 9. Revised Inclusion Criterion 10. Revised Inclusion Criterion 3. Revised Exclusion Criterion 11. Revised Exclusion Criterion 28. Revised last bullet to "Treatment with a disallowed medication, other investigational drug within 5 half-lives or 30 days before Screening, whichever time is longer, or the use of an investigational device within 30 days before Screening is prohibited." Revised first sentence to "Prior use of an investigational drug within 5 half-lives or 30 days before Screening, whichever time is longer, or the use of an investigational device within 30 days before Screening is prohibited." Moved examples of contraceptive methods with a failure rate of <1% per year under new subheading "Highly Effective Methods of Birth Control." Revised the time between Visits 1 and 2 to be ≥2 weeks. Clarified that a plasma PK sample is not required at the EoS visit. Clarified that a plasma PK sample is not required at the EoS visit. Changes implemented for non-US sites: - Added Exclusion Criterion 29 to exclude participants who participated in an earlier part of the current study (ie, Part 1 or 2) within 6 months of dosing for a subsequent part (ie, Part 2 or 3); - Revised Exclusion Criterion 7.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported