



Clinical trial results:

A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Assess the Safety, Pharmacokinetics, and Efficacy of KPL-404 in Subjects with Moderate to Severe, Active Rheumatoid Arthritis with Inadequate Response or Intolerance to at Least One Biologic Disease modifying Anti-rheumatic Drug or a Janus Kinase Inhibitor

Summary

EudraCT number	2022-000169-42
Trial protocol	DE CZ HU BG
Global end of trial date	06 May 2024

Results information

Result version number	v1 (current)
This version publication date	21 May 2025
First version publication date	21 May 2025

Trial information

Trial identification

Sponsor protocol code	KPL-404-C211
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05198310
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 155,963

Notes:

Sponsors

Sponsor organisation name	Kiniksa Pharmaceuticals, Ltd.
Sponsor organisation address	c/o Kiniksa Pharmaceuticals Corp., 100 Hayden Avenue, Lexington, MA, United States, 02421
Public contact	Clinical Trials Manager, Kiniksa Pharmaceuticals, Ltd., +1 7814319100, studyinfo@Kiniksa.com
Scientific contact	Clinical Trials Manager, Kiniksa Pharmaceuticals, Ltd., +1 7814319100, studyinfo@Kiniksa.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	06 May 2024
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	06 May 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Cohorts 1 and 2: To evaluate the dose response relationship as measured by safety, tolerability, and pharmacokinetics (PK) of multiple subcutaneous (SC) doses of KPL-404 versus placebo.

Cohorts 3 and 4: To evaluate the efficacy of multiple SC doses of KPL-404 versus placebo for the treatment of rheumatoid arthritis (RA).

Protection of trial subjects:

Before initiating a trial, the investigator/Institution must obtain approval/favorable opinion from the IRB or Independent Ethics Committee (IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures, and any other written information to be provided to subjects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 November 2021
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: 21
Country: Number of subjects enrolled	Bulgaria: 6
Country: Number of subjects enrolled	Czechia: 14
Country: Number of subjects enrolled	Hungary: 17
Country: Number of subjects enrolled	Georgia: 14
Country: Number of subjects enrolled	South Africa: 18
Country: Number of subjects enrolled	United States: 55
Worldwide total number of subjects	145
EEA total number of subjects	58

Notes:

Subjects enrolled per age group

In utero	0
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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)	95
From 65 to 84 years	50
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study included a screening period of up to 4 weeks.

Period 1

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

Blinding implementation details:

This was a double-blind, placebo-controlled study. Investigators, the remaining clinical site staff, and the subjects were blinded to treatment throughout the course of the study. The Sponsor was also blinded to subject treatment assignment while each cohort's enrollment and subject follow-up was ongoing.

Arms

Are arms mutually exclusive?	Yes
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Arm title	Cohort 1 KPL-404 2 mg/kg every 2 weeks (q2wk)
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Arm description:

KPL-404 2 mg/kg subcutaneous (SC) q2wk for 12 weeks

Arm type	Experimental
Investigational medicinal product name	KPL-404
Investigational medicinal product code	
Other name	abiprubart
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Cohort 1: 2 mg/kg KPL-404 q2wk

Arm title	Cohort 2 KPL-404 5 mg/kg q2wk
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Arm description:

KPL-404 5 mg/kg SC q2wk for 12 weeks

Arm type	Experimental
Investigational medicinal product name	KPL-404
Investigational medicinal product code	
Other name	abiprubart
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Cohort 2: 5 mg/kg KPL-404 q2wk

Arm title	Cohort 1/2 Placebo
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Arm description:

Placebo SC q2wk for 12 weeks

Arm type	Placebo
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Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo volume was to be matched to abiprubart at the corresponding dosage level.

Arm title	Cohort 3 KPL-404 5 mg/kg qwk
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Arm description:

KPL-404 5 mg/kg SC once weekly (qwk) for 12 weeks

Arm type	Experimental
Investigational medicinal product name	KPL-404
Investigational medicinal product code	
Other name	abiprubart
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Cohort 3: 5 mg/kg SC qwk

Arm title	Cohort 3 KPL-404 5 mg/kg q2wk
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Arm description:

KPL-404 5 mg/kg SC q2wk with alternating weekly administrations of KPL-404 or placebo SC for 12 weeks

Arm type	Experimental
Investigational medicinal product name	KPL-404
Investigational medicinal product code	
Other name	abiprubart
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Cohort 3: 5 mg/kg SC q2w (weekly dosing with alternating administration of KPL 404 q2wk or placebo q2wk)

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo volume was to be matched to abiprubart at the corresponding dosage level.

In Cohort 3 in the q2wk dosage group, placebo was to be alternated with abiprubart administration.

Arm title	Cohort 3 Placebo
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Arm description:

Placebo SC qwk for 12 weeks

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo volume was to be matched to abiprubart at the corresponding dosage level.

In Cohort 3 in the placebo group, placebo was to be given qwk.

Arm title	Cohort 4: KPL-404 400 mg q4wk
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Arm description:

KPL-404 SC every 4 weeks (q4wk) for 12 weeks: 600 mg loading dose at baseline followed by 400 mg at Weeks 4 and 8

Arm type	Experimental
Investigational medicinal product name	KPL-404
Investigational medicinal product code	
Other name	abiprubart
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Cohort 4: KPL-404 SC q4wk (600 mg loading dose followed by maintenance dosing 400 mg q4wk at Weeks 4 and 8)

Arm title	Cohort 4 Placebo
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Arm description:

Placebo SC q4wk for 12 weeks

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo volume was to be matched to abiprubart at the corresponding dosage level.

In Cohort 4, placebo was to be administered as a volume-equivalent of abiprubart: a loading dose (i.e., 3 mL) followed by maintenance dosing (i.e., 2 mL) q4wk.

Number of subjects in period 1	Cohort 1 KPL-404 2 mg/kg every 2 weeks (q2wk)	Cohort 2 KPL-404 5 mg/kg q2wk	Cohort 1/2 Placebo
Started	6	6	4
Completed	6	5	4
Not completed	0	1	0
Consent withdrawn by subject	-	-	-
Lost to follow-up	-	1	-

Number of subjects in period 1	Cohort 3 KPL-404 5 mg/kg qwk	Cohort 3 KPL-404 5 mg/kg q2wk	Cohort 3 Placebo
Started	27	25	26
Completed	25	25	24
Not completed	2	0	2
Consent withdrawn by subject	2	-	2
Lost to follow-up	-	-	-

Number of subjects in period 1	Cohort 4: KPL-404 400 mg q4wk	Cohort 4 Placebo
Started	31	20
Completed	30	17
Not completed	1	3
Consent withdrawn by subject	1	3
Lost to follow-up	-	-

Baseline characteristics

Reporting groups

Reporting group title	Cohort 1 KPL-404 2 mg/kg every 2 weeks (q2wk)
Reporting group description:	
KPL-404 2 mg/kg subcutaneous (SC) q2wk for 12 weeks	
Reporting group title	Cohort 2 KPL-404 5 mg/kg q2wk
Reporting group description:	
KPL-404 5 mg/kg SC q2wk for 12 weeks	
Reporting group title	Cohort 1/2 Placebo
Reporting group description:	
Placebo SC q2wk for 12 weeks	
Reporting group title	Cohort 3 KPL-404 5 mg/kg qwk
Reporting group description:	
KPL-404 5 mg/kg SC once weekly (qwk) for 12 weeks	
Reporting group title	Cohort 3 KPL-404 5 mg/kg q2wk
Reporting group description:	
KPL-404 5 mg/kg SC q2wk with alternating weekly administrations of KPL-404 or placebo SC for 12 weeks	
Reporting group title	Cohort 3 Placebo
Reporting group description:	
Placebo SC qwk for 12 weeks	
Reporting group title	Cohort 4: KPL-404 400 mg q4wk
Reporting group description:	
KPL-404 SC every 4 weeks (q4wk) for 12 weeks: 600 mg loading dose at baseline followed by 400 mg at Weeks 4 and 8	
Reporting group title	Cohort 4 Placebo
Reporting group description:	
Placebo SC q4wk for 12 weeks	

Reporting group values	Cohort 1 KPL-404 2 mg/kg every 2 weeks (q2wk)	Cohort 2 KPL-404 5 mg/kg q2wk	Cohort 1/2 Placebo
Number of subjects	6	6	4
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	56.8	56.3	59.8
standard deviation	± 15.59	± 13.29	± 13.05
Gender categorical			
Units: Subjects			
Female	5	5	4
Male	1	1	0
Ethnicity			
Units: Subjects			
Hispanic or Latino	1	4	2
Not Hispanic or Latino	5	2	2
Race			

Units: Subjects			
Asian	0	0	0
Black or African American	1	0	0
White	5	6	4

Reporting group values	Cohort 3 KPL-404 5 mg/kg qwk	Cohort 3 KPL-404 5 mg/kg q2wk	Cohort 3 Placebo
Number of subjects	27	25	26
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	58.5	60.0	57.6
standard deviation	± 9.68	± 10.10	± 9.90
Gender categorical			
Units: Subjects			
Female	22	20	24
Male	5	5	2
Ethnicity			
Units: Subjects			
Hispanic or Latino	2	3	6
Not Hispanic or Latino	25	22	20
Race			
Units: Subjects			
Asian	1	0	0
Black or African American	1	2	2
White	25	23	24

Reporting group values	Cohort 4: KPL-404 400 mg q4wk	Cohort 4 Placebo	Total
Number of subjects	31	20	145
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	58.8	58.3	
standard deviation	± 9.45	± 11.81	-
Gender categorical			
Units: Subjects			
Female	25	15	120
Male	6	5	25
Ethnicity			
Units: Subjects			
Hispanic or Latino	5	1	24
Not Hispanic or Latino	26	19	121
Race			
Units: Subjects			
Asian	2	2	5
Black or African American	3	1	10
White	26	17	130

End points

End points reporting groups

Reporting group title	Cohort 1 KPL-404 2 mg/kg every 2 weeks (q2wk)
Reporting group description: KPL-404 2 mg/kg subcutaneous (SC) q2wk for 12 weeks	
Reporting group title	Cohort 2 KPL-404 5 mg/kg q2wk
Reporting group description: KPL-404 5 mg/kg SC q2wk for 12 weeks	
Reporting group title	Cohort 1/2 Placebo
Reporting group description: Placebo SC q2wk for 12 weeks	
Reporting group title	Cohort 3 KPL-404 5 mg/kg qwk
Reporting group description: KPL-404 5 mg/kg SC once weekly (qwk) for 12 weeks	
Reporting group title	Cohort 3 KPL-404 5 mg/kg q2wk
Reporting group description: KPL-404 5 mg/kg SC q2wk with alternating weekly administrations of KPL-404 or placebo SC for 12 weeks	
Reporting group title	Cohort 3 Placebo
Reporting group description: Placebo SC qwk for 12 weeks	
Reporting group title	Cohort 4: KPL-404 400 mg q4wk
Reporting group description: KPL-404 SC every 4 weeks (q4wk) for 12 weeks: 600 mg loading dose at baseline followed by 400 mg at Weeks 4 and 8	
Reporting group title	Cohort 4 Placebo
Reporting group description: Placebo SC q4wk for 12 weeks	

Primary: Cohorts 1 and 2: Number of Participants With Treatment-Emergent Adverse Events (TEAEs)

End point title	Cohorts 1 and 2: Number of Participants With Treatment-Emergent Adverse Events (TEAEs) ^{[1][2]}
End point description: Adverse event (AE): any untoward medical occurrence, which does not necessarily have a causal relationship with this treatment. Serious AE (SAE): AE that: results in death; is immediately life-threatening; requires in-patient hospitalization/prolongation of existing hospitalization; results in persistent or significant disability/incapacity; results in a congenital abnormality/birth defect; is an important medical event. TEAEs: AEs not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug during treatment period. AE severity: mild (Grade [Gr] 1); moderate (Gr 2); severe (Gr 3); potentially life threatening (Gr 4); death (Gr 5). AEs of special interest: thrombosis, serious infection, serious and non-serious bacterial infections, eye disorders, and anaphylaxis/hypersensitivity reactions.	
Safety Population: Randomized participants who received ≥ 1 dose of study drug.	
End point type	Primary
End point timeframe: From first dose of study drug to 24 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: Statistical analyses are presented in the data table.

[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: Per protocol, this endpoint applied only to Cohorts 1 and 2.

End point values	Cohort 1 KPL-404 2 mg/kg every 2 weeks (q2wk)	Cohort 2 KPL-404 5 mg/kg q2wk	Cohort 1/2 Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	4	
Units: participants				
TEAEs	2	2	3	
Drug-related TEAEs	1	1	1	
TEAEs by maximum severity	2	2	3	
Maximum Severity = Mild	1	1	1	
Maximum Severity = Moderate	1	1	2	
Maximum Severity = Severe	0	0	0	
Maximum Severity = Potentially Life threatening	0	0	0	
Maximum Severity = Fatal	0	0	0	
Serious TEAEs	0	0	0	
Drug-related SAEs	0	0	0	
TEAEs leading to death	0	0	0	
TEAEs leading to dose interruption	1	1	0	
TEAEs leading to treatment discontinuation	0	0	0	
TEAEs of special interest	0	0	0	
Injection site reactions	0	1	0	

Statistical analyses

No statistical analyses for this end point

Primary: Cohorts 1 and 2: Maximum Serum Concentration (C_{max})

End point title	Cohorts 1 and 2: Maximum Serum Concentration (C _{max}) ^{[3][4]}
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End point description:

Participants treated with KPL-404, with an evaluable PK sample at given time point.

End point type	Primary
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End point timeframe:

Days 1 (Dose 1) and 57 (Dose 4)

Notes:

[3] - 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: Statistical analyses are presented in the data table.

[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: Per protocol, this endpoint applied only to Cohorts 1 and 2.

End point values	Cohort 1 KPL-404 2 mg/kg every 2 weeks (q2wk)	Cohort 2 KPL-404 5 mg/kg q2wk		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5 ^[5]	6 ^[6]		
Units: µg/mL				
arithmetic mean (standard deviation)				
Day 1; n=5, 6	7.57 (± 7.52)	28.0 (± 13.5)		
Day 57; n=3, 6	17.8 (± 13.9)	68.3 (± 25.1)		

Notes:

[5] - n=number of participants with an assessment at given timepoint.

[6] - n=number of participants with an assessment at given timepoint.

Statistical analyses

No statistical analyses for this end point

Primary: Cohorts 1 and 2: Area Under the Serum Concentration-time Curve From Time 0 to the End of the Dosing Interval (AUCtau)

End point title	Cohorts 1 and 2: Area Under the Serum Concentration-time Curve From Time 0 to the End of the Dosing Interval (AUCtau) ^[7] ^[8]
End point description:	Participants treated with KPL-404, with an evaluable PK sample at given time point.
End point type	Primary
End point timeframe:	Days 1 (Dose 1) and 57 (Dose 4)

Notes:

[7] - 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: Statistical analyses are presented in the data table.

[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: Per protocol, this endpoint applied only to Cohorts 1 and 2.

End point values	Cohort 1 KPL-404 2 mg/kg every 2 weeks (q2wk)	Cohort 2 KPL-404 5 mg/kg q2wk		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5 ^[9]	6 ^[10]		
Units: µg·day/mL				
arithmetic mean (standard deviation)				
Day 1; n=5, 6	59.0 (± 51.1)	303 (± 148)		
Day 57; n=3, 6	162 (± 114)	810 (± 290)		

Notes:

[9] - n=number of participants with an assessment at given timepoint.

[10] - n=number of participants with an assessment at given timepoint.

Statistical analyses

No statistical analyses for this end point

Primary: Cohort 3 and 4: Change From Baseline in Disease Activity Score of 28 Joints Using C-reactive Protein (DAS28-CRP) at Week 12

End point title	Cohort 3 and 4: Change From Baseline in Disease Activity Score of 28 Joints Using C-reactive Protein (DAS28-CRP) at Week 12 ^[11]
End point description:	
DAS28 is a measure based on assessment of 28 joints for tenderness and swelling (tender and swollen joint counts). DAS28-CRP is derived using differential weighting given to 4 components: tender joint count (range: 0-28), swollen joint count (range: 0-28), patient global assessment (recorded on a visual analog scale [VAS] scale of 0-100 mm), and CRP (milligram per liter). DAS28-CRP score ranges from 0 to 9.4. The lower the DAS28-CRP score is, the better the participant has response (remission = score < 2.6, low disease activity = score < 3.2). A negative value in change from BL indicates an improvement.	
Modified Intent-to-Treat (mITT) population: All randomized participants who received at least one dose of study drug and who had at least one postbaseline assessment for the primary efficacy endpoint.	
End point type	Primary
End point timeframe:	
Baseline, Week 12	

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: Per protocol, this endpoint applied only to Cohorts 3 and 4.

End point values	Cohort 3 KPL-404 5 mg/kg qwk	Cohort 3 KPL-404 5 mg/kg q2wk	Cohort 3 Placebo	Cohort 4: KPL-404 400 mg q4wk
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	25	26	31
Units: score on a scale				
least squares mean (standard error)	-2.17 (± 0.216)	-1.96 (± 0.220)	-1.61 (± 0.218)	-1.87 (± 0.331)

End point values	Cohort 4 Placebo			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: score on a scale				
least squares mean (standard error)	-1.30 (± 0.338)			

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Cohort 3 Placebo v Cohort 3 KPL-404 5 mg/kg qwk
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.047 ^[12]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.57

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.13
upper limit	-0.01
Variability estimate	Standard error of the mean
Dispersion value	0.281

Notes:

[12] - Analyzed using ANCOVA model with baseline value and stratification factor (≤ 1 vs. ≥ 2 classes of advanced targeted therapies) as covariates.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Cohort 3 KPL-404 5 mg/kg q2wk v Cohort 3 Placebo
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2124 ^[13]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.92
upper limit	0.21
Variability estimate	Standard error of the mean
Dispersion value	0.282

Notes:

[13] - Analyzed using ANCOVA model with baseline value and stratification factor (≤ 1 vs. ≥ 2 classes of advanced targeted therapies) as covariates.

Statistical analysis title	Statistical Analysis 3
Comparison groups	Cohort 4 Placebo v Cohort 4: KPL-404 400 mg q4wk
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1091 ^[14]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.28
upper limit	0.13
Variability estimate	Standard error of the mean
Dispersion value	0.352

Notes:

[14] - Analyzed using ANCOVA model with baseline value and stratification factor (≤ 1 vs. ≥ 2 classes of advanced targeted therapies) as covariates.

Secondary: Cohorts 1 and 2: Change From Baseline in DAS28-CRP at Week 12

End point title	Cohorts 1 and 2: Change From Baseline in DAS28-CRP at Week
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End point description:

DAS28 is a measure based on assessment of 28 joints for tenderness and swelling (tender and swollen joint counts). DAS28-CRP is derived using differential weighting given to 4 components: tender joint count (range: 0-28), swollen joint count (range: 0-28), patient global assessment (recorded on a visual analog scale [VAS] scale of 0-100 mm), and CRP (milligram per liter). DAS28-CRP score ranges from 0 to 9.4. The lower the DAS28-CRP score is, the better the participant has response (remission = score < 2.6, low disease activity = score < 3.2). A negative value in change from BL indicates an improvement.

Modified Intent-to-Treat (mITT) population: All randomized participants who received at least one dose of study drug and who had at least one postbaseline assessment for the primary efficacy endpoint.

End point type	Secondary
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End point timeframe:	
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Baseline, Week 12	
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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: Per protocol, this endpoint applied only to Cohorts 1 and 2.

End point values	Cohort 1 KPL-404 2 mg/kg every 2 weeks (q2wk)	Cohort 2 KPL-404 5 mg/kg q2wk	Cohort 1/2 Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	6	4	
Units: score on a scale				
arithmetic mean (standard deviation)	-3.16 (± 1.130)	-3.44 (± 1.450)	-1.09 (± 1.373)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Cohort 1 KPL-404 2 mg/kg every 2 weeks (q2wk) v Cohort 1/2 Placebo
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0312
Method	t-test

Statistical analysis title	Statistical Analysis 2
Comparison groups	Cohort 1/2 Placebo v Cohort 2 KPL-404 5 mg/kg q2wk
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0338
Method	t-test

Secondary: Cohorts 3 and 4: Number of Participants With TEAEs

End point title	Cohorts 3 and 4: Number of Participants With TEAEs ^[16]
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End point description:

Adverse event (AE): any untoward medical occurrence, which does not necessarily have a causal relationship with this treatment. Serious AE (SAE): AE that: results in death; is immediately life-threatening; requires in-patient hospitalization/prolongation of existing hospitalization; results in persistent or significant disability/incapacity; results in a congenital abnormality/birth defect; is an important medical event. TEAEs: AEs not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug during treatment period. AE severity: mild (Grade [Gr] 1); moderate (Gr 2); severe (Gr 3); potentially life threatening (Gr 4); death (Gr 5). AEs of special interest: thrombosis, serious infection, serious and non-serious bacterial infections, eye disorders, and anaphylaxis/hypersensitivity reactions.

Safety Population: Randomized participants who received ≥ 1 dose of study drug.

End point type	Secondary
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End point timeframe:

From first dose of study drug to 24 weeks

Notes:

[16] - 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: Per protocol, this endpoint applied only to Cohorts 3 and 4.

End point values	Cohort 3 KPL-404 5 mg/kg qwk	Cohort 3 KPL-404 5 mg/kg q2wk	Cohort 3 Placebo	Cohort 4: KPL-404 400 mg q4wk
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	25	26	31
Units: participants				
TEAEs	12	6	8	9
Drug-related TEAEs	2	2	2	3
TEAEs by maximum severity	12	6	8	9
Maximum Severity = Mild	8	3	4	4
Maximum Severity = Moderate	4	3	4	5
Maximum Severity = Severe	0	0	0	0
Maximum Severity = Potentially Life threatening	0	0	0	0
Maximum Severity = Fatal	0	0	0	0
Serious TEAEs	1	0	0	0
Drug-related SAEs	0	0	0	0
TEAEs leading to death	0	0	0	0
TEAEs leading to dose interruption	1	0	1	0
TEAEs leading to treatment discontinuation	0	0	0	1
TEAEs of special interest	1	1	0	1
Injection site reactions	1	1	0	2

End point values	Cohort 4 Placebo			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: participants				
TEAEs	8			
Drug-related TEAEs	1			

TEAEs by maximum severity	8			
Maximum Severity = Mild	5			
Maximum Severity = Moderate	3			
Maximum Severity = Severe	0			
Maximum Severity = Potentially Life threatening	0			
Maximum Severity = Fatal	0			
Serious TEAEs	0			
Drug-related SAEs	0			
TEAEs leading to death	0			
TEAEs leading to dose interruption	0			
TEAEs leading to treatment discontinuation	1			
TEAEs of special interest	2			
Injection site reactions	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 3 and 4: Cmax

End point title Cohort 3 and 4: Cmax^[17]

End point description:

Participants treated with KPL-404, with an evaluable PK sample at given time point.

End point type Secondary

End point timeframe:

Days 1 (Dose 1) and 57 (Dose 4 or 8)

Notes:

[17] - 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: Per protocol, this endpoint applied only to Cohorts 3 and 4.

End point values	Cohort 3 KPL-404 5 mg/kg qwk	Cohort 3 KPL-404 5 mg/kg q2wk	Cohort 4: KPL-404 400 mg q4wk	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27 ^[18]	25 ^[19]	30 ^[20]	
Units: µg/mL				
arithmetic mean (standard deviation)				
Day 1; n=27, 25, 30	27.1 (± 11.0)	29.4 (± 10.3)	48.5 (± 18.2)	
Day 57; n=22, 25, 27	145 (± 41.0)	70.9 (± 21.5)	45.6 (± 21.4)	

Notes:

[18] - n=number of participants with an assessment at given timepoint.

[19] - n=number of participants with an assessment at given timepoint.

[20] - n=number of participants with an assessment at given timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 3 and 4: AUCtau

End point title	Cohort 3 and 4: AUCtau ^[21]
End point description:	Participants treated with KPL-404, with an evaluable PK sample at given time point.
End point type	Secondary
End point timeframe:	Days 1 (Dose 1) and 57 (Dose 4 or 8)
Notes:	<p>[21] - 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.</p> <p>Justification: Per protocol, this endpoint applied only to Cohorts 3 and 4.</p>

End point values	Cohort 3 KPL-404 5 mg/kg qwk	Cohort 3 KPL-404 5 mg/kg q2wk	Cohort 4: KPL-404 400 mg q4wk	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	25	30	
Units: µg·day/mL				
arithmetic mean (standard deviation)				
Day 1; n=27, 25, 30	139 (± 63.4)	310 (± 105)	873 (± 363)	
Day 57; n=22, 25, 27	975 (± 291)	849 (± 267)	843 (± 466)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving American College of Rheumatology 20% (ACR20) Response at Week 12

End point title	Percentage of Participants Achieving American College of Rheumatology 20% (ACR20) Response at Week 12
End point description:	<p>An ACR20 response is defined as at least a 20% improvement in both tender joint count (TJC) and swollen joint count (SJC), and at least a 20% improvement in three of the following five criteria: patient global assessment (PGA), physician global assessment (PhGA), functional ability measure [Health Assessment Questionnaire (HAQ)], patient's assessment of pain (visual analog scale; VAS) and C-reactive protein (CRP).</p> <p>mITT population: All randomized participants who received at least one dose of study drug and who had at least one post-baseline assessment for the primary efficacy endpoint.</p>
End point type	Secondary
End point timeframe:	Baseline, Week 12

End point values	Cohort 1 KPL-404 2 mg/kg every 2 weeks (q2wk)	Cohort 2 KPL-404 5 mg/kg q2wk	Cohort 1/2 Placebo	Cohort 3 KPL-404 5 mg/kg qwk
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	4	27
Units: percentage of participants				
number (not applicable)	100	83.3	25.0	74.1

End point values	Cohort 3 KPL-404 5 mg/kg q2wk	Cohort 3 Placebo	Cohort 4: KPL-404 400 mg q4wk	Cohort 4 Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	26	31	20
Units: percentage of participants				
number (not applicable)	60.0	50.0	80.6	40.0

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Cohort 1 KPL-404 2 mg/kg every 2 weeks (q2wk) v Cohort 1/2 Placebo
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0333
Method	Fisher exact test

Statistical analysis title	Statistical Analysis 2
Comparison groups	Cohort 1/2 Placebo v Cohort 2 KPL-404 5 mg/kg q2wk
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1905
Method	Fisher exact test

Statistical analysis title	Statistical Analysis 3
Comparison groups	Cohort 3 KPL-404 5 mg/kg qwk v Cohort 3 Placebo

Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0716
Method	CMH test
Parameter estimate	Odds ratio (OR)
Point estimate	2.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	9.65

Statistical analysis title	Statistical Analysis 4
Comparison groups	Cohort 3 Placebo v Cohort 3 KPL-404 5 mg/kg q2wk
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.471
Method	CMH test
Parameter estimate	Odds ratio (OR)
Point estimate	1.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	4.67

Statistical analysis title	Statistical Analysis 5
Comparison groups	Cohort 4: KPL-404 400 mg q4wk v Cohort 4 Placebo
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0057
Method	CMH test
Parameter estimate	Odds ratio (OR)
Point estimate	6.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.62
upper limit	22.88

Secondary: Percentage of Participants Achieving American College of Rheumatology

50% (ACR50) Response at Week 12

End point title	Percentage of Participants Achieving American College of Rheumatology 50% (ACR50) Response at Week 12
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End point description:

An ACR50 response is defined as at least a 50% improvement in both tender joint count (TJC) and swollen joint count (SJC), and at least a 50% improvement in three of the following five criteria: patient global assessment (PGA), physician global assessment (PhGA), functional ability measure [Health Assessment Questionnaire (HAQ)], patient's assessment of pain (visual analog scale; VAS) and C-reactive protein (CRP).

mITT population: All randomized participants who received at least one dose of study drug and who had at least one post-baseline assessment for the primary efficacy endpoint.

End point type	Secondary
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End point timeframe:

Baseline, Week 12

End point values	Cohort 1 KPL-404 2 mg/kg every 2 weeks (q2wk)	Cohort 2 KPL-404 5 mg/kg q2wk	Cohort 1/2 Placebo	Cohort 3 KPL-404 5 mg/kg qwk
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	4	27
Units: percentage of participants				
number (not applicable)	66.7	16.7	0	33.3

End point values	Cohort 3 KPL-404 5 mg/kg q2wk	Cohort 3 Placebo	Cohort 4: KPL-404 400 mg q4wk	Cohort 4 Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	26	31	20
Units: percentage of participants				
number (not applicable)	36.0	23.1	32.3	30.0

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Cohort 1 KPL-404 2 mg/kg every 2 weeks (q2wk) v Cohort 1/2 Placebo
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0762
Method	Fisher exact test

Statistical analysis title	Statistical Analysis 2
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Comparison groups	Cohort 1/2 Placebo v Cohort 2 KPL-404 5 mg/kg q2wk
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact test

Statistical analysis title	Statistical Analysis 3
Comparison groups	Cohort 3 KPL-404 5 mg/kg qwk v Cohort 3 Placebo
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4172
Method	CMH test
Parameter estimate	Odds ratio (OR)
Point estimate	1.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	5.62

Statistical analysis title	Statistical Analysis 4
Comparison groups	Cohort 3 Placebo v Cohort 3 KPL-404 5 mg/kg q2wk
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3144
Method	CMH test
Parameter estimate	Odds ratio (OR)
Point estimate	1.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	6.45

Statistical analysis title	Statistical Analysis 5
Comparison groups	Cohort 4: KPL-404 400 mg q4wk v Cohort 4 Placebo

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.956
Method	CMH test
Parameter estimate	Odds ratio (OR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	3.39

Secondary: Percentage of Participants Achieving American College of Rheumatology 70% (ACR70) Response at Week 12

End point title	Percentage of Participants Achieving American College of Rheumatology 70% (ACR70) Response at Week 12
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End point description:

An ACR70 response is defined as at least a 70% improvement in both tender joint count (TJC) and swollen joint count (SJC), and at least a 70% improvement in three of the following five criteria: patient global assessment (PGA), physician global assessment (PhGA), functional ability measure [Health Assessment Questionnaire (HAQ)], patient's assessment of pain (visual analog scale; VAS) and C-reactive protein (CRP).

mITT population: All randomized participants who received at least one dose of study drug and who had at least one post-baseline assessment for the primary efficacy endpoint.

End point type	Secondary
End point timeframe:	
Baseline, Week 12	

End point values	Cohort 1 KPL-404 2 mg/kg every 2 weeks (q2wk)	Cohort 2 KPL-404 5 mg/kg q2wk	Cohort 1/2 Placebo	Cohort 3 KPL-404 5 mg/kg qwk
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	4	27
Units: percentage of participants				
number (not applicable)	33.3	16.7	0	7.4

End point values	Cohort 3 KPL-404 5 mg/kg q2wk	Cohort 3 Placebo	Cohort 4: KPL-404 400 mg q4wk	Cohort 4 Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	26	31	20
Units: percentage of participants				
number (not applicable)	20.0	3.8	9.7	25.0

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Cohort 1 KPL-404 2 mg/kg every 2 weeks (q2wk) v Cohort 1/2 Placebo
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4667
Method	Fisher exact test

Statistical analysis title	Statistical Analysis 2
Comparison groups	Cohort 2 KPL-404 5 mg/kg q2wk v Cohort 1/2 Placebo
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact test

Statistical analysis title	Statistical Analysis 3
Comparison groups	Cohort 3 KPL-404 5 mg/kg qwk v Cohort 3 Placebo
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5789
Method	CMH test
Parameter estimate	Odds ratio (OR)
Point estimate	1.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	22.3

Statistical analysis title	Statistical Analysis 4
Comparison groups	Cohort 3 Placebo v Cohort 3 KPL-404 5 mg/kg q2wk

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0799
Method	CMH test
Parameter estimate	Odds ratio (OR)
Point estimate	6.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	60.1

Statistical analysis title	Statistical Analysis 5
Comparison groups	Cohort 4: KPL-404 400 mg q4wk v Cohort 4 Placebo
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1034
Method	CMH test
Parameter estimate	Odds ratio (OR)
Point estimate	0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	1.35

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 28 weeks

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	27.0
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Reporting groups

Reporting group title	Cohort 1 KPL-404 2 mg/kg q2wk
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Reporting group description:

KPL-404 2 mg/kg subcutaneous (SC) every 2 weeks (q2wk) for 12 weeks

Reporting group title	Cohort 2 KPL-404 5 mg/kg q2wk
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Reporting group description:

KPL-404 5 mg/kg SC q2wk for 12 weeks

Reporting group title	Cohort 1/2 Placebo
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Reporting group description:

Placebo SC q2wk for 12 weeks

Reporting group title	Cohort 3 KPL-404 5 mg/kg qwk
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Reporting group description:

KPL-404 5 mg/kg SC once weekly (qwk) for 12 weeks

Reporting group title	Cohort 3 KPL-404 5 mg/kg q2wk
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Reporting group description:

KPL-404 5 mg/kg SC q2wk with alternating weekly administrations of KPL-404 or placebo SC for 12 weeks

Reporting group title	Cohort 3 Placebo
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Reporting group description:

Placebo SC qwk for 12 weeks

Reporting group title	Cohort 4: KPL-404 400 mg q4wk
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Reporting group description:

KPL-404 SC every 4 weeks (q4wk) for 12 weeks: 600 mg loading dose at baseline followed by 400 mg at Weeks 4 and 8

Reporting group title	Cohort 4 Placebo
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Reporting group description:

Placebo SC q4wk for 12 weeks

Serious adverse events	Cohort 1 KPL-404 2 mg/kg q2wk	Cohort 2 KPL-404 5 mg/kg q2wk	Cohort 1/2 Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Ear and labyrinth disorders			
Sudden hearing loss			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 4 (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
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 4 (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	Cohort 3 KPL-404 5 mg/kg qwk	Cohort 3 KPL-404 5 mg/kg q2wk	Cohort 3 Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	1 / 26 (3.85%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Ear and labyrinth disorders			
Sudden hearing loss			
subjects affected / exposed	1 / 27 (3.70%)	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			
Hyponatraemia			
subjects affected / exposed	0 / 27 (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

Serious adverse events	Cohort 4: KPL-404 400 mg q4wk	Cohort 4 Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 31 (0.00%)	0 / 20 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Ear and labyrinth disorders			
Sudden hearing loss			
subjects affected / exposed	0 / 31 (0.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			

Hyponatraemia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 0	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	Cohort 1 KPL-404 2 mg/kg q2wk	Cohort 2 KPL-404 5 mg/kg q2wk	Cohort 1/2 Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 6 (33.33%)	2 / 6 (33.33%)	3 / 4 (75.00%)
Investigations			
Fibrin D dimer increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Animal scratch			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Sinus headache			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Injection site erythema			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0

Injection site pain subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 4 (0.00%) 0
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 4 (0.00%) 0
Abdominal discomfort subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	1 / 6 (16.67%) 1	0 / 4 (0.00%) 0
Reproductive system and breast disorders			
Prostatitis subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 4 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0	0 / 4 (0.00%) 0
Dyspnoea subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 4 (0.00%) 0
Interstitial lung disease subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	1 / 4 (25.00%) 1
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	1 / 4 (25.00%) 1
Arthritis subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 4 (0.00%) 0
Pain in extremity subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1	0 / 6 (0.00%) 0	0 / 4 (0.00%) 0
Rheumatoid arthritis			

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 6 (0.00%) 0	0 / 4 (0.00%) 0
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 6 (16.67%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Campylobacter infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 6 (16.67%)	2 / 4 (50.00%)
occurrences (all)	0	1	2
Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hyperuricaemia			

subjects affected / exposed	0 / 6 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort 3 KPL-404 5 mg/kg qwk	Cohort 3 KPL-404 5 mg/kg q2wk	Cohort 3 Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 27 (22.22%)	5 / 25 (20.00%)	4 / 26 (15.38%)
Investigations			
Fibrin D dimer increased			
subjects affected / exposed	0 / 27 (0.00%)	0 / 25 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Animal scratch			
subjects affected / exposed	0 / 27 (0.00%)	0 / 25 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 27 (7.41%)	0 / 25 (0.00%)	1 / 26 (3.85%)
occurrences (all)	2	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	2 / 26 (7.69%)
occurrences (all)	1	0	2
Sinus headache			
subjects affected / exposed	0 / 27 (0.00%)	0 / 25 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 27 (0.00%)	0 / 25 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Injection site erythema			
subjects affected / exposed	0 / 27 (0.00%)	0 / 25 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Injection site pain			
subjects affected / exposed	0 / 27 (0.00%)	2 / 25 (8.00%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			

Diarrhoea subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	0 / 25 (0.00%) 0	0 / 26 (0.00%) 0
Abdominal discomfort subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	0 / 25 (0.00%) 0	0 / 26 (0.00%) 0
Reproductive system and breast disorders Prostatitis subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	0 / 25 (0.00%) 0	0 / 26 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Interstitial lung disease subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0 0 / 27 (0.00%) 0 0 / 27 (0.00%) 0	0 / 25 (0.00%) 0 0 / 25 (0.00%) 0 0 / 25 (0.00%) 0	0 / 26 (0.00%) 0 0 / 26 (0.00%) 0 0 / 26 (0.00%) 0
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Arthritis subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) Rheumatoid arthritis subjects affected / exposed occurrences (all)	1 / 27 (3.70%) 1 0 / 27 (0.00%) 0 0 / 27 (0.00%) 0 0 / 27 (0.00%) 0	0 / 25 (0.00%) 0 0 / 25 (0.00%) 0 0 / 25 (0.00%) 0 2 / 25 (8.00%) 2	0 / 26 (0.00%) 0 0 / 26 (0.00%) 0 0 / 26 (0.00%) 0 1 / 26 (3.85%) 1
Infections and infestations			

COVID-19			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	1 / 26 (3.85%)
occurrences (all)	1	0	1
Campylobacter infection			
subjects affected / exposed	0 / 27 (0.00%)	0 / 25 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 25 (4.00%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	0 / 27 (0.00%)	2 / 25 (8.00%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
Sinusitis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 25 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 27 (0.00%)	1 / 25 (4.00%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Bronchitis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 25 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	4 / 27 (14.81%)	0 / 25 (0.00%)	2 / 26 (7.69%)
occurrences (all)	4	0	3
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	1 / 27 (3.70%)	0 / 25 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Hyperuricaemia			
subjects affected / exposed	0 / 27 (0.00%)	0 / 25 (0.00%)	0 / 26 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort 4: KPL-404 400 mg q4wk	Cohort 4 Placebo	
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Total subjects affected by non-serious adverse events subjects affected / exposed	5 / 31 (16.13%)	8 / 20 (40.00%)	
Investigations Fibrin D dimer increased subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	1 / 20 (5.00%) 1	
Injury, poisoning and procedural complications Animal scratch subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	0 / 20 (0.00%) 0	
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1	0 / 20 (0.00%) 0	
Nervous system disorders Headache subjects affected / exposed occurrences (all) Sinus headache subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1 0 / 31 (0.00%) 0	0 / 20 (0.00%) 0 0 / 20 (0.00%) 0	
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Injection site erythema subjects affected / exposed occurrences (all) Injection site pain subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0 0 / 31 (0.00%) 0 1 / 31 (3.23%) 1	0 / 20 (0.00%) 0 0 / 20 (0.00%) 0 0 / 20 (0.00%) 0	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Abdominal discomfort	1 / 31 (3.23%) 1	0 / 20 (0.00%) 0	

subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	0 / 20 (0.00%) 0	
Reproductive system and breast disorders Prostatitis subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	1 / 20 (5.00%) 1	
Respiratory, thoracic and mediastinal disorders Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Interstitial lung disease subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0 0 / 31 (0.00%) 0 0 / 31 (0.00%) 0	1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 0 / 20 (0.00%) 0	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Arthritis subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) Rheumatoid arthritis subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0 0 / 31 (0.00%) 0 0 / 31 (0.00%) 0 2 / 31 (6.45%) 2	0 / 20 (0.00%) 0 1 / 20 (5.00%) 1 0 / 20 (0.00%) 0 1 / 20 (5.00%) 1	
Infections and infestations COVID-19 subjects affected / exposed occurrences (all) Campylobacter infection	0 / 31 (0.00%) 0	0 / 20 (0.00%) 0	

subjects affected / exposed	0 / 31 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Gastroenteritis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	2 / 31 (6.45%)	1 / 20 (5.00%)	
occurrences (all)	2	1	
Sinusitis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 20 (0.00%)	
occurrences (all)	0	0	
Urinary tract infection			
subjects affected / exposed	2 / 31 (6.45%)	2 / 20 (10.00%)	
occurrences (all)	4	2	
Bronchitis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	2 / 31 (6.45%)	0 / 20 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	1 / 31 (3.23%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Hyperuricaemia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 August 2021	<ul style="list-style-type: none">• Study design was revised to increase volume of safety data available to inform the dose escalation decision.• A 2-sided type 1 error rate of 0.1 was specified for the efficacy analysis.• Additional detail was provided regarding statistical methodology.• Description of Safety Review Committee (SRC) was revised to increase its independence and prevent bias in study management.• More stringent stopping rules were provided allowing for safety review.• Description of efficacy endpoints was clarified.
09 December 2021	<ul style="list-style-type: none">• Description of primary endpoints was clarified.• Text was added to reflect changes to study design specific to Cohort 4, including an increase in sample size from 60 to 75 participants.• Text was added to reflect changes to randomization and stratification factors based on changes to entry criteria.• Study schema was updated to include changes to Cohort 4.• Contraception requirements were clarified.• Text was added to distinguish between treatment discontinuation, withdrawal of consent, and lost-to-follow up.• Text was added to clarify details relative to study drug packaging and labeling that appear elsewhere.• Criteria for assessments that do not need to be done in a specific order were updated.• Text was updated to better describe the clinical outcome assessment measurements being collected.• Synovial biopsy substudy was deleted.• Timing for collection of anti-drug antibody (ADA) blood samples was clarified.• Cannabinoids were deleted from urine drug screen.• Description of adverse event of special interest (AESIs) was clarified.• Interim analysis plans were clarified.
12 August 2022	<ul style="list-style-type: none">• Sponsor personnel were updated.• Study design was changed to facilitate investigation of the 5 mg/kg SC dose level (qwk and q2wk).• Alpha 0.05 was selected for the determination of sample size to provide a tight control of type 1 error.• Study objectives, blinding rules, randomization schema, and study schema were revised to align with the new study design.• The SRC schedule for Cohort 3 was revised to provide safety oversight for the proof-of-concept Cohort 3 portion of the study.• Relatedness language was revised.• Dose justification was revised to include pharmacodynamics and additional pharmacokinetics information.• Schedule of Activities was added for Cohort 3.• Blood collection for circulating transcriptomic biomarkers were removed for Cohorts 2 and 3.

31 March 2023	<ul style="list-style-type: none"> • Sponsor personnel was updated. • Text was modified to clarify the end of study follow-up period and collection of AEs/SAEs. • Study Schema was updated to correctly represent new elements of the protocol amendment. • Body weight limit was increased to allow expansion of RA participant population. • Inclusion criteria were updated to reflect available advanced targeted therapies for treatment of RA. • CRP limit inclusion criterion was updated to reflect and align with clinical trial practice in RA. • Rheumatoid factor (RF) and/or anti-citrullinated protein antibody (ACPA) inclusion criteria were updated to provide operational flexibility to investigational sites. • Inclusion criterion for potential participants already receiving opiate analgesia was updated to a dose no greater than 50 MME/day. • Exclusion criterion was updated to accept participants with TB who had been appropriately treated. • Stratification factors were updated to stratify based on the number of prior classes of advanced targeted therapies to which they had demonstrated inadequate therapeutic response (≤ 1 vs ≥ 2). • Blinding language was clarified to allow treatment assignment unblinding of completed cohorts. • Text was added clarifying IP administration within protocol-specified time window. • Collection of medication history was revised for clarity. • Interim analysis text was revised. • Analysis method was changed to better account for the new stratification scheme.
28 June 2023	<ul style="list-style-type: none"> • The objectives and endpoints, sample size, randomization, rationale, dose levels and dose administration, Schedule of Assessments, and Study Schema were updated/added to include the new Cohort 4. • Text was added to describe when SRC meetings would begin and how frequently they would occur for Cohorts 3 and 4. • Text was added to describe when participants should return for an end-of-treatment visit following premature discontinuation of treatment. • Text was added to clarify the mITT population definition and to align this definition with the Statistical Analysis Plan. • Text was revised to clarify the definitions of low disease activity and complete response and to align these definitions with the Statistical Analysis Plan. • Text was added to align with the Statistical Analysis Plan definitions of TEAEs.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported