Clinical trial results:
A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, ACTIVE REFERENCE (ADALIMUMAB) STUDY EVALUATING THE EFFICACY AND SAFETY OF BIMEKIZUMAB IN THE TREATMENT OF SUBJECTS WITH ACTIVE PSORIATIC ARTHRITIS

Summary

EudraCT number	2017-002322-20
Trial protocol	DE GB BE FR HU ES CZ IT
Global end of trial date	11 July 2022

Results information

Result version number	v1
This version publication date	23 July 2023
First version publication date	23 July 2023

Trial information

Trial identification

Sponsor protocol code	PA0010

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03895203
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB Biopharma SRL
Sponsor organisation address	Allée de la Recherche 60, Brussels, Belgium, 1070
Public contact	Clin Trial Reg & Results Disclosure, UCB BIOSCIENCES GmbH, clinicaltrials@ucb.com
Scientific contact	Clin Trial Reg & Results Disclosure, UCB BIOSCIENCES GmbH, clinicaltrials@ucb.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 July 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Demonstrate the clinical efficacy of bimekizumab administered subcutaneously (sc) compared with placebo in the treatment of subjects with active Psoriatic Arthritis (PsA), as assessed by the American College of Rheumatology 50% Improvement (ACR50) response.

Protection of trial subjects:

Patients were closely monitored and were expected to be treated for any worsening as per investigator judgement. Moreover, rescue medication could be added if patient was not having benefit of therapy, as per investigator discretion.

Background therapy:

No background therapy.

Evidence for comparator:

Adalimumab

Actual start date of recruitment	03 April 2019
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	Australia: 65
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	Czechia: 115
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 76
Country: Number of subjects enrolled	Hungary: 30
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Japan: 23
Country: Number of subjects enrolled	Poland: 276
Country: Number of subjects enrolled	Russian Federation: 113
Country: Number of subjects enrolled	Spain: 35
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 92
Worldwide total number of subjects	852
EEA total number of subjects	546

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)	763
From 65 to 84 years	89
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study started to enroll participants in April 2019 and concluded in July 2022.

Pre-assignment

Screening details:

The Participant Flow refers to the Randomized Set (RS) which consists of enrolled participants that have been randomized and Active Treatment-Blind Set (ATS) which consists of all participants who received at least 1 dose of active treatment (Bimekizumab [BKZ] or Adalimumab [ADA]) during the Active Treatment-Blind Period (ATP) (Week 16 and after).

Period 1

Period 1 title	Double-Blind Treatment Period: 16 Weeks
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received placebo during the 16-weeks Double-Blind Treatment Period (DBP).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received placebo Q4W at prespecified time points.

Arm title	BKZ 160 mg Q4W

Arm description:

Participants received BKZ 160 milligrams (mg) subcutaneous (SC) every 4 weeks (Q4W) during the 16-weeks DBP.

Arm type	Experimental
Investigational medicinal product name	Bimekizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received BKZ 160 mg Q4W at prespecified time points.

Arm title	ADA 40 mg Q2W

Arm description:

Participants received ADA 40 mg SC every 2 weeks (Q2W) during the 16-weeks DBP.

Arm type	Active comparator

Investigational medicinal product name	Adalimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received ADA 40 mg SC Q2W at prespecified time points.

Number of subjects in period 1	Placebo	BKZ 160 mg Q4W	ADA 40 mg Q2W
Started	281	431	140
Enthesitis: PA0010/11 pooled population	106 [1]	249 [2]	0 [3]
Dactylitis: PA0010/11 pooled population	47 [4]	90 [5]	0 [6]
Completed	271	415	137
Not completed	10	16	3
Consent withdrawn by subject	4	6	1
PHQ-9 Score elevated	-	1	-
Adverse event, non-fatal	2	8	2
Site terminated	-	1	-
Lost to follow-up	2	-	-
Lack of efficacy	2	-	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This milestone is created for data presentation for clarity of dactylitis-free state, planned for the pooled PA0010 (NCT03895203) and PA0011 (NCT03896581) population.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This milestone is created for data presentation for clarity of enthesitis-free state, planned for the pooled PA0010 (NCT03895203) and PA0011 (NCT03896581) population.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This milestone is created for data presentation for clarity of dactylitis-free state, planned for the pooled PA0010 (NCT03895203) and PA0011 (NCT03896581) population.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This milestone is created for data presentation for clarity of enthesitis-free state, planned for the pooled PA0010 (NCT03895203) and PA0011 (NCT03896581) population.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This milestone is created for data presentation for clarity of dactylitis-free state, planned for the pooled PA0010 (NCT03895203) and PA0011 (NCT03896581) population.

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This milestone is created for data presentation for clarity of enthesitis-free state, planned for the pooled PA0010 (NCT03895203) and PA0011 (NCT03896581) population.

Period 2

Period 2 title	Active Treatment-Blind Period: 36 Weeks
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo/BKZ 160 mg Q4W

Arm description:

After the 16-weeks DBP, participants initially randomized to placebo received BKZ 160 mg SC Q4W during the 36-weeks ATP.

Arm type	Experimental
Investigational medicinal product name	Bimekizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received BKZ 160 mg Q4W at prespecified time points.

Arm title	BKZ 160 mg Q4W/BKZ 160 mg Q4W

Arm description:

After the 16-weeks DBP, participants initially randomized to BKZ 160 mg continued to receive BKZ 160 mg SC Q4W during the 36-weeks ATP.

Arm type	Experimental
Investigational medicinal product name	Bimekizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received BKZ 160 mg Q4W at prespecified time points.

Arm title	ADA 40 mg Q2W/ADA 40 mg Q2W

Arm description:

After the 16-weeks DBP, participants initially randomized to ADA 40 mg continued to receive ADA 40 mg SC Q2W during the 36-weeks ATP.

Arm type	Active comparator
Investigational medicinal product name	Adalimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received ADA 40 mg SC Q2W at prespecified time points.

Number of subjects in period 2[7]	Placebo/BKZ 160 mg Q4W	BKZ 160 mg Q4W/BKZ 160 mg Q4W	ADA 40 mg Q2W/ADA 40 mg Q2W
Started	271	414	136
Completed	257	387	125
Not completed	14	27	11
Adverse event, serious fatal	1	-	-
Consent withdrawn by subject	4	9	2
Adverse event, non-fatal	5	9	4
Withdrawal due to Subject Decision	1	-	-
Subject Moving Out of Area	-	-	1
COVID-19 Pandemic Circumstances	1	-	-
Lost to follow-up	1	3	-
Lack of efficacy	1	6	4

Notes:

[7] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Eligible participants who continued to receive active treatment at Week 16 (participants not on treatment at Week 16 but continued in the study were excluded) were started in ATP.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo during the 16-weeks Double-Blind Treatment Period (DBP).	
Reporting group title	BKZ 160 mg Q4W
Reporting group description:	
Participants received BKZ 160 milligrams (mg) subcutaneous (SC) every 4 weeks (Q4W) during the 16-weeks DBP.	
Reporting group title	ADA 40 mg Q2W
Reporting group description:	
Participants received ADA 40 mg SC every 2 weeks (Q2W) during the 16-weeks DBP.	

Reporting group values	Placebo	BKZ 160 mg Q4W	ADA 40 mg Q2W
Number of subjects	281	431	140
Age Categorical Units: Participants			
<=18 years	0	0	0
Between 18 and 65 years	255	386	122
>=65 years	26	45	18
Age Continuous Units: Years			
arithmetic mean	48.7	48.5	49.0
standard deviation	± 11.7	± 12.6	± 12.8
Sex: Female, Male Units: Participants			
Female	154	230	69
Male	127	201	71

Reporting group values	Total		
Number of subjects	852		
Age Categorical Units: Participants			
<=18 years	0		
Between 18 and 65 years	763		
>=65 years	89		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Participants			
Female	453		
Male	399		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo during the 16-weeks Double-Blind Treatment Period (DBP).	
Reporting group title	BKZ 160 mg Q4W
Reporting group description:	
Participants received BKZ 160 milligrams (mg) subcutaneous (SC) every 4 weeks (Q4W) during the 16-weeks DBP.	
Reporting group title	ADA 40 mg Q2W
Reporting group description:	
Participants received ADA 40 mg SC every 2 weeks (Q2W) during the 16-weeks DBP.	
Reporting group title	Placebo/BKZ 160 mg Q4W
Reporting group description:	
After the 16-weeks DBP, participants initially randomized to placebo received BKZ 160 mg SC Q4W during the 36-weeks ATP.	
Reporting group title	BKZ 160 mg Q4W/BKZ 160 mg Q4W
Reporting group description:	
After the 16-weeks DBP, participants initially randomized to BKZ 160 mg continued to receive BKZ 160 mg SC Q4W during the 36-weeks ATP.	
Reporting group title	ADA 40 mg Q2W/ADA 40 mg Q2W
Reporting group description:	
After the 16-weeks DBP, participants initially randomized to ADA 40 mg continued to receive ADA 40 mg SC Q2W during the 36-weeks ATP.	

Primary: Percentage of Participants With an American College of Rheumatology (ACR) 50 response at Week 16

End point title	Percentage of Participants With an American College of Rheumatology (ACR) 50 response at Week 16
End point description:	
ACR50 response rate: 50% or greater improvement of arthritis from Baseline. Those who met 3 conditions for improvement from Baseline met ACR50 response criteria: Tender joint count (0-68 joints) greater than or equal (≥)50% improvement; Swollen joint count (0-66 joints) ≥50% improvement; ≥50% improvement in at least 3 of 5 below: Physician global assessment of disease activity (visual analog scale [VAS] [0-100 millimeter {mm}; no symptoms to severe]), Patient global assessment of disease activity (VAS-[0-100 mm; no limitation of normal activities to very poor]), Patient assessment of pain (VAS-[0-100 mm; no pain to most severe]), Health Assessment Questionnaire-Disability Index for degree of difficulty (20 queries from 8 domains of daily living activities total scored 0-3, 0 = less disability) High-sensitivity C-reactive protein (hsCRP). Analysis set: RS. Non-responders: Those who missed ACR50 data at Week 16 or who discontinued study before Week 16 regardless of data present or not.	
End point type	Primary
End point timeframe:	
Week 16	

End point values	Placebo	BKZ 160 mg Q4W	ADA 40 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	281	431	140	
Units: percentage of participants				
number (not applicable)	10.0	43.9	45.7	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v BKZ 160 mg Q4W
Number of subjects included in analysis	712
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	7.082
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.583
upper limit	10.943

Secondary: Change from Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 16

End point title	Change from Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 16[1]

End point description:

HAQ-DI contains 20 items that measured degree of difficulty experienced in following 8 categories of daily living activities: dressing and grooming (2 items), arising (2 items), eating (3 items), walking (2 items), hygiene (3 items), reach (2 items), grip (3 items), and common daily activities (3 items). Each question was scored 0-3 (0 = without any difficulty, 1 = with some difficulty, 2 = with much difficulty, and 3 = unable to do). The overall HAQ-DI total score was calculated by dividing the sum of the highest category scores (0 to 24) by the number of categories with at least 1 question answered. Total score ranges from 0 (no difficulty) to 3 (maximum difficulty). A lower HAQ-DI score indicated an improvement in function. A negative value in change from baseline indicated an improvement. RS consisted of all enrolled participants who had been randomized. Missing data and non-missing data after treatment discontinuation were imputed using reference based multiple imputation.

End point type	Secondary

End point timeframe:

Baseline, Week 16

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Descriptive statistics for ADA 40 mg reference arm for few endpoints was not calculated and reported since reference based imputation analysis method was used with Placebo as reference. Inferential Statistics for ADA 40 mg reference arm was not calculated and reported as no formal comparison was planned.

End point values	Placebo	BKZ 160 mg Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	281	431		
Units: score on a scale				
arithmetic mean (standard error)	-0.0881 (± 0.0273)	-0.2567 (± 0.0208)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v BKZ 160 mg Q4W
Number of subjects included in analysis	712
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least square (LS) mean difference
Point estimate	-0.187
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.249
upper limit	-0.125

Secondary: Percentage of Participants With a Psoriasis Area Severity Index (PASI) 90 response at Week 4 in the subgroup of participants with psoriasis (PSO) involving at least 3% body surface area (BSA) at Baseline

End point title	Percentage of Participants With a Psoriasis Area Severity Index (PASI) 90 response at Week 4 in the subgroup of participants with psoriasis (PSO) involving at least 3% body surface area (BSA) at Baseline

End point description:

The PASI90 response assessments are based on at least 90% improvement in PASI score from Baseline. Body divided into 4 areas: head, arms, trunk to groin, and legs to top of buttocks. Assignment of average score for redness, thickness, and scaling for each of 4 body areas with score of 0 (clear) to 4 (very marked). Determining percentage of skin covered with PSO for each of body areas and converting to 0 to 6 scale. Final PASI = average redness, thickness, and scaliness of psoriatic skin lesions, multiplied by involved psoriasis area score of respective section, and weighted by percentage of person's affected skin for respective section. Minimum possible PASI score is 0 = no disease, maximum score is 72 = maximal disease. Subset of RS with psoriasis involving at least 3% BSA at Baseline. Those who have missing PASI90 data at Week 4 or who discontinued study treatment before Week 4 regardless of whether they had data or not are considered as non-responders.

End point type	Secondary

End point timeframe:

Baseline, Week 4

End point values	Placebo	BKZ 160 mg Q4W	ADA 40 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	140	217	68	
Units: percentage of participants				
number (not applicable)	4.3	19.8	7.4	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Short Form 36-item Health Survey (SF-36) Physical Component Summary (PCS) at Week 16

End point title	Change from Baseline in the Short Form 36-item Health Survey (SF-36) Physical Component Summary (PCS) at Week 16[2]

End point description:

SF-36:36-item generic health-related Quality of Life instrument uses recall period of 4 weeks. Questionnaire has 36 questions composing scale represent 8 domains:physical functioning;role physical;bodily pain;general health;vitality;social functioning;role emotional;mental health. Scores for 8 domains were combined into two summary scores: PCS and mental component summary (MCS) scores. Component summary scores and 8 domains have been computed raw/observed score to norm-based T-score metric (mean=50, standard deviation=10), raw score min=0(worst), max=100(best). Individual respondent's score outside T-score range of 45 to 55 was considered outside average range and when considering group-level data, score below 47 was considered indicative of impaired functioning within health domain or dimension. Positive value in change from Baseline indicated improvement. Analysis set RS. Missing and non-missing data after treatment discontinuation imputed using reference based multiple imputation.

End point type	Secondary

End point timeframe:

Baseline, Week 16

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Descriptive statistics for ADA 40 mg reference arm for few endpoints was not calculated and reported since reference based imputation analysis method was used with Placebo as reference. Inferential Statistics for ADA 40 mg reference arm was not calculated and reported as no formal comparison was planned.

End point values	Placebo	BKZ 160 mg Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	281	431		
Units: score on a scale				
arithmetic mean (standard error)	2.326 (± 0.478)	6.219 (± 0.402)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v BKZ 160 mg Q4W

Number of subjects included in analysis	712
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	4.337
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.229
upper limit	5.444

Secondary: Percentage of Participants With a Minimal Disease Activity (MDA) at Week 16

End point title	Percentage of Participants With a Minimal Disease Activity (MDA) at Week 16

End point description:

Participant considered having achieved MDA if participant fulfills at least 5 of following 7 criteria: Tender joint count (0-68 joints) less than or equal to (≤) 1; Swollen joint count (0-66 joints) ≤ 1; PASI ≤ 1 or BSA ≤ 3: In PASI, body divided into four parts, head and neck, upper limb, trunk and lower limbs. Each area assessed for erythema, induration and scaling, each rated on scale of 0 to 4. Total score ranges from 0 (no disease) to 72 (maximal disease)]; Patient's Assessment of Arthritis Pain ≤ 15 [VAS on scale of 0 (no pain) to 100 (severe pain)]; Patient's Global Assessment of Disease Activity ≤ 20 [VAS on scale of 0 (very well) to 100 (very poor)]; HAQ-DI score ≤ 0.5, HAQ-DI score ranges from 0 (no difficulty) to 3 (maximum difficulty); Leeds Enthesitis Index score ≤ 1 for participants with enthesitis at baseline. Analysis Set: RS. Non-responders: Who missed MDA at Week 16 or discontinued study before Week 16 regardless of data present or not.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo	BKZ 160 mg Q4W	ADA 40 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	281	431	140	
Units: percentage of participants				
number (not applicable)	13.2	45.0	45.0	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v BKZ 160 mg Q4W

Number of subjects included in analysis	712
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	5.447
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.668
upper limit	8.088

Secondary: Percentage of Participants With a PASI90 response at Week 16 in the subgroup of participants with PSO involving at least 3% BSA at Baseline

End point title	Percentage of Participants With a PASI90 response at Week 16 in the subgroup of participants with PSO involving at least 3% BSA at Baseline

End point description:

The PASI90 response assessments are based on at least 90% improvement in PASI score from Baseline. Body divided into 4 areas: head, arms, trunk to groin, and legs to top of buttocks. Assignment of an average score for redness, thickness, and scaling for each of the 4 body areas with a score of 0 (clear) to 4 (very marked). Determining the percentage of skin covered with PSO for each of the body areas and converting to a 0 to 6 scale. Final PASI= average redness, thickness, and scaliness of psoriatic skin lesions, multiplied by involved psoriasis area score of respective section, and weighted by percentage of person's affected skin for respective section. The minimum possible PASI score is 0= no disease, the maximum score is 72= maximal disease. Subset of RS with psoriasis involving at least 3% BSA at Baseline. Those who have missing PASI90 data at Week 16 or who discontinued study treatment before Week 16 regardless of whether they had data or not are considered as non-responders.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Placebo	BKZ 160 mg Q4W	ADA 40 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	140	217	68	
Units: percentage of participants				
number (not applicable)	2.9	61.3	41.2	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v BKZ 160 mg Q4W

Number of subjects included in analysis	357
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	63.039
Confidence interval	
level	95 %
sides	2-sided
lower limit	22.211
upper limit	178.918

Secondary: Percentage of Participants With an Enthesitis-free state in the Leeds Enthesitis Index (LEI) at Week 16 in the subgroup of participants with enthesitis at Baseline in the pooled population of PA0010 and PA0011

End point title	Percentage of Participants With an Enthesitis-free state in the Leeds Enthesitis Index (LEI) at Week 16 in the subgroup of participants with enthesitis at Baseline in the pooled population of PA0010 and PA0011[3]

End point description:

Presence of enthesitis was assessed in the subgroup of participants with enthesitis by palpation on the lateral epicondyles of the humerus (elbows), medial femoral epicondyles (knees), and Achilles tendons (heels) bilaterally and scored as 0 (no tenderness) and 1 (tenderness) at Baseline. The LEI consists of 6 items, 3 for the right part and 3 for the left part of the body. LEI is derived as the sum of the enthesitis score over the 6 sites mentioned above. The total score ranges from 0 to 6, higher scores indicates greater degree of enthesitis. As pre-specified in the SAP, the subgroup of participants with enthesitis at Baseline in the pooled population of PA0010 and PA0011 (NCT03896581) were included for the analysis of outcome measure. Participants who have missing LEI at Week 16 or who discontinued study treatment before Week 16 regardless of whether they had data or not are considered as non achieving entheistis free-state.

End point type	Secondary

End point timeframe:

Baseline, Week 16

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: Descriptive statistics for ADA 40 mg reference arm for few endpoints was not calculated and reported since reference based imputation analysis method was used with Placebo as reference. Inferential Statistics for ADA 40 mg reference arm was not calculated and reported as no formal comparison was planned.

End point values	Placebo	BKZ 160 mg Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106	249		
Units: percentage of participants				
number (not applicable)	34.9	49.8		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v BKZ 160 mg Q4W
Number of subjects included in analysis	355
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.904
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.18
upper limit	3.074

Secondary: Change from Baseline in Van der Heijde modified Total Sharp Score (vdHmTSS) in participants with elevated hs-CRP and/or at least 1 bone erosion at Baseline at Week 16

End point title	Change from Baseline in Van der Heijde modified Total Sharp Score (vdHmTSS) in participants with elevated hs-CRP and/or at least 1 bone erosion at Baseline at Week 16[4]

End point description:

The degree of joint damage was assessed using the vdHmTSS by quantifying the extent of bone erosions and joint space narrowing for 64 and 52 joints, respectively. The vdHmTSS ranges from 0 to 528, with higher scores representing greater damage. The Radiographic Set (RAS) consisted of all participants in the RS who received at least 1 dose of investigational medicinal product (IMP) and have a valid radiographic image of the hands and feet (with an assessment performed by at least the 2 reviewers) at Screening. Missing data and non-missing data preceded by a study treatment discontinuation were imputed using reference based multiple imputation. Here, number of participants analyzed included RAS set with elevated hs-CRP and/or with at least one bone erosion at Baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 16

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: Descriptive statistics for ADA 40 mg reference arm for few endpoints was not calculated and reported since reference based imputation analysis method was used with Placebo as reference. Inferential Statistics for ADA 40 mg reference arm was not calculated and reported as no formal comparison was planned.

End point values	Placebo	BKZ 160 mg Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	227	361		
Units: score on a scale				
arithmetic mean (standard error)	0.36 (± 0.10)	0.04 (± 0.05)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v BKZ 160 mg Q4W
Number of subjects included in analysis	588
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	-0.327
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.524
upper limit	-0.13

Secondary: Percentage of Participants With an American College of Rheumatology (ACR) 20 response at Week 16

End point title	Percentage of Participants With an American College of Rheumatology (ACR) 20 response at Week 16

End point description:

ACR20 response rate:20% or greater improvement of arthritis relative to Baseline. Those who met following 3 conditions for improvement from Baseline were classified as meeting ACR20 criteria: 1. ≥ 20% improvement in 68-tender joint count; 2. ≥ 20% improvement in 66-swollen joint count; and 3. ≥ 20% improvement in at least 3 of 5 parameters: Physician global assessment of disease activity (100 mm VAS[0 = no symptoms; 100 = severe symptoms]), Patient global assessment of disease activity (100 mm VAS [0 = no limitation of normal activities; 100 = very poor]), Patient assessment of pain (100 mm VAS [0 = no pain; 100 = most severe pain]), HAQ-DI assessed degree of difficulty experienced in 8 domains of daily living activities (20 questions), its score (0-3) computed from item scores, lower scores indicated less disability, hsCRP. Analysis set: RS. Non-responders: Those who missed ACR20 data at Week 16 or who discontinued study before Week 16 regardless of data present or not.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo	BKZ 160 mg Q4W	ADA 40 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	281	431	140	
Units: percentage of participants				
number (not applicable)	23.8	62.2	68.6	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a Dactylitis-free state based on the

Leeds Dactylitis Index (LDI) at Week 16 in the subgroup of participants with dactylitis at Baseline in the pooled population of PA0010 and PA0011

End point title	Percentage of Participants With a Dactylitis-free state based on the Leeds Dactylitis Index (LDI) at Week 16 in the subgroup of participants with dactylitis at Baseline in the pooled population of PA0010 and PA0011[5]

End point description:

LDI: measures dactylitis using circumference of involved digits and control digits and tenderness of involved digits. Digits affected by dactylitis are defined those with 10% difference in ratio of circumference of affected digit to contralateral digit. Control digit is either contralateral digit (digit on opposite hand or foot). Ratio of circumference between affected digit and control digit is multiplied by tenderness score for affected digit. Results from each involved digit are summed to provide final LDI score. Higher LDI indicates worse dactylitis. Tenderness score (0 = no tenderness, 1 = tender). As pre-specified in the SAP, subgroup of participants with dactylitis at Baseline in pooled population of PA0010 and PA0011 (NCT03896581) were included for analysis of outcome measure. Non achieving dactylitis free-state: who have missing LDI at Week 16 or discontinued study before Week 16 regardless of whether they have data or not.

End point type	Secondary

End point timeframe:

Baseline, Week 16

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: Descriptive statistics for ADA 40 mg reference arm for few endpoints was not calculated and reported since reference based imputation analysis method was used with Placebo as reference. Inferential Statistics for ADA 40 mg reference arm was not calculated and reported as no formal comparison was planned.

End point values	Placebo	BKZ 160 mg Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	90		
Units: percentage of participants				
number (not applicable)	51.1	75.6		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v BKZ 160 mg Q4W
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.437
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.559
upper limit	7.574

Secondary: Percentage of Participants With an American College of Rheumatology (ACR) 70 response at Week 16

End point title	Percentage of Participants With an American College of Rheumatology (ACR) 70 response at Week 16

End point description:

ACR70 response rate: 70% or greater improvement of arthritis relative to Baseline. Participants who met following 3 conditions for improvement from Baseline were classified as meeting ACR70 response criteria: 1. ≥ 70% improvement in 68-tender joint count; 2. ≥ 70% improvement in 66-swollen joint count; and 3. ≥ 70% improvement in at least 3 of 5 following parameters: Physician global assessment of disease activity (100 mm VAS [0 = no symptoms;100 = severe symptoms]), Patient global assessment of disease activity (100 mm VAS [0 = no limitation of normal activities;100 = very poor]), Patient assessment of pain (100 mm VAS [0 = no pain; 100 = most severe pain]), HAQ-DI assessed degree of difficulty experienced in 8 domains of daily living activities (20 questions), its score (0-3) computed from item scores, lower scores indicated less disability, hsCRP. RS. Non-responders: Those who missed ACR70 data at Week 16 or who discontinued study before Week 16 regardless of data present or not.

End point type	Secondary

End point timeframe:

Week 16

End point values	Placebo	BKZ 160 mg Q4W	ADA 40 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	281	431	140	
Units: percentage of participants				
number (not applicable)	4.3	24.4	27.9	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Van der Heijde modified Total Sharp Score (vdHmTSS) in the overall population at Week 16

End point title	Change from Baseline in Van der Heijde modified Total Sharp Score (vdHmTSS) in the overall population at Week 16[6]

End point description:

The degree of joint damage was assessed using the vdHmTSS by quantifying the extent of bone erosions and joint space narrowing for 64 and 52 joints, respectively. The vdHmTSS ranges from 0 to 448, with higher scores representing greater damage. The RAS consisted of all participants in the RS who received at least 1 dose of IMP and have a valid radiographic image of the hands and feet (with an assessment performed by at least the 2 reviewers) at Screening. Missing data and non-missing data preceded by a study treatment discontinuation were imputed using reference based multiple imputation.

End point type	Secondary

End point timeframe:

Baseline, Week 16

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: Descriptive statistics for ADA 40 mg reference arm for few endpoints was not calculated and reported since reference based imputation analysis method was used with Placebo as reference. Inferential Statistics for ADA 40 mg reference arm was not calculated and reported as no formal comparison was planned.

End point values	Placebo	BKZ 160 mg Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	269	420		
Units: score on a scale				
arithmetic mean (standard error)	0.32 (± 0.09)	0.04 (± 0.04)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v BKZ 160 mg Q4W
Number of subjects included in analysis	689
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.281
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.452
upper limit	-0.111

Secondary: Percentage of Participants With an Investigator Global Assessment (IGA) response defined as score of 0(clear) or 1(almost clear) AND at least a 2-grade reduction from Baseline at Week 4 in the subset of participants with psoriatic skin lesions at Baseline

End point title	Percentage of Participants With an Investigator Global Assessment (IGA) response defined as score of 0(clear) or 1(almost clear) AND at least a 2-grade reduction from Baseline at Week 4 in the subset of participants with psoriatic skin lesions at Baseline

End point description:

IGA measured the overall severity of PSO using the following 5-point scale and score was rated as 0 = clear (No signs of PSO; post-inflammatory hyperpigmentation may be present), 1 = almost clear (No thickening; normal to pink coloration; no to minimal focal scaling), 2 = mild (Just detectable to mild thickening; pink to light red coloration; predominately fine scaling), 3 = moderate (Clearly distinguishable to moderate thickening; dull to bright red, moderate scaling), and 4 = severe (Severe thickening with hard edges; bright to deep dark red coloration; severe/coarse scaling covering almost all or all lesions). The IGA response is defined as score of 0 (clear) or 1 (almost clear) with at least a 2-category improvement relative to Baseline. Subset of study participants in RS with psoriatic skin lesions at Baseline. Non-responders: Participants who had missing data at the Week 4 or who discontinued study treatment before or at the Week 4 regardless of whether they had data or not.

End point type	Secondary

End point timeframe:

Baseline, Week 4

End point values	Placebo	BKZ 160 mg Q4W	ADA 40 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	129	204	62	
Units: percentage of participants				
number (not applicable)	3.9	28.9	11.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Psoriatic Arthritis Impact of Disease-12 (PsAID-12) total score at Week 16

End point title	Change from Baseline in Psoriatic Arthritis Impact of Disease-12 (PsAID-12) total score at Week 16

End point description:

The PsAID-12 is a patient-reported outcome measure for assessing the impact of Psoriatic Arthritis (PsA) in 12 physical and psychological domains, including pain, fatigue, skin problems, work and/or leisure activities, functional capacity, discomfort, sleep disturbance, coping, anxiety/fear/uncertainty, embarrassment and/or shame, social participation, and depression. Each domain is assessed with a single question using a 0 to 10 numerical rating scale. Each domain score was multiplied by a weighting factor and the results were then summed to provide the total score. The total score ranged from 0 to 10, with higher scores indicating a worse status. A negative change from baseline indicates improvement. RS consisted of all enrolled participants who had been randomized. Missing data and non-missing data preceded by a study treatment discontinuation were imputed using reference based multiple imputation.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Placebo	BKZ 160 mg Q4W	ADA 40 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	281	431	140	
Units: score on a scale				
arithmetic mean (standard error)	-0.53 (± 0.10)	-1.83 (± 0.09)	-2.14 (± 0.16)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With an IGA response defined as score of 0 (clear) or 1 (almost clear) AND at least a 2-grade reduction from Baseline at Week 16 in the subset of participants with psoriatic skin lesions at Baseline

End point title	Percentage of Participants With an IGA response defined as score of 0 (clear) or 1 (almost clear) AND at least a 2-grade reduction from Baseline at Week 16 in the subset of participants with psoriatic skin lesions at Baseline

End point description:

IGA measured the overall severity of PSO using the following 5-point scale and score was rated as 0 = clear (No signs of PSO; post-inflammatory hyperpigmentation may be present), 1 = almost clear (No thickening; normal to pink coloration; no to minimal focal scaling), 2 = mild (Just detectable to mild thickening; pink to light red coloration; predominately fine scaling), 3 = moderate (Clearly distinguishable to moderate thickening; dull to bright red, moderate scaling), and 4 = severe (Severe thickening with hard edges; bright to deep dark red coloration; severe/coarse scaling covering almost all or all lesions). The IGA response is defined as score of 0 (clear) or 1 (almost clear) with at least a 2-category improvement relative to Baseline. Subset of study participants in RS with psoriatic skin lesions at Baseline. Non-responders: Participants who had missing data at the Week 16 or who discontinued study treatment before or at the Week 16 regardless of whether they had data or not.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Placebo	BKZ 160 mg Q4W	ADA 40 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	129	204	62	
Units: percentage of participants				
number (not applicable)	3.9	50.5	33.9	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With an Enthesitis-free state based on the Spondyloarthritis Research Consortium of Canada (SPARCC) index at Week 16 in the subgroup of participants with enthesitis at Baseline

End point title	Percentage of Participants With an Enthesitis-free state based on the Spondyloarthritis Research Consortium of Canada (SPARCC) index at Week 16 in the subgroup of participants with enthesitis at Baseline

End point description:

Presence of enthesitis was assessed in subgroup of participants with enthesitis at Baseline. The SPARCC index measures severity of enthesitis through assessment of 16 sites, 8 for right part and 8 for left part of the body: greater trochanter (right/left), quadriceps tendon insertion into patella (right/left), patellar ligament insertion into patella and tibial tuberosity (right/left), achilles tendon insertion (right/left), plantar fascia insertion (right/left), medial and lateral epicondyles (right/left), and supraspinatus insertion (right/left). Tenderness on examination is recorded as either present (1) or absent (0) for each of 16 sites, for an mention- average range of 0 (no enthesitis) to 16 (severe enthesitis). Subset of study participants in RS with SPARCC > 0 at Baseline. Participants who had missing SPARCC at Week 16 or who discontinued study treatment before Week 16 regardless of whether they had data or not are considered as not achieving enthesitis free-state.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Placebo	BKZ 160 mg Q4W	ADA 40 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	90	166	44	
Units: percentage of participants				
number (not applicable)	35.6	50.0	52.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Patient's Assessment of Arthritis Pain (PtAAP) at Week 16

End point title	Change from Baseline in the Patient's Assessment of Arthritis Pain (PtAAP) at Week 16

End point description:

The PtAAP VAS is part of the American College of Rheumatology core set of measures in arthritis. Participants assessed their arthritis pain using a VAS ranging from 0 (no pain) to 100 (most severe pain). A negative change from baseline indicates improvement. RS consisted of all enrolled participants who had been randomized. Missing data and non-missing data preceded by a study treatment discontinuation were imputed using reference based multiple imputation.

End point type	Secondary

End point timeframe:

Baseline, Week 16

End point values	Placebo	BKZ 160 mg Q4W	ADA 40 mg Q2W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	281	431	140	
Units: score on a scale				
arithmetic mean (standard error)	-6.3 (± 1.5)	-23.6 (± 1.3)	-25.7 (± 2.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with TEAEs leading to withdrawal from IMP during the study

End point title	Percentage of Participants with TEAEs leading to withdrawal from IMP during the study

End point description:

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE could therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. TEAEs were defined as any AEs with an onset date on or after the date of first IMP administration and within 140 days after the final dose of IMP. The Safety Set consisted of all participants who received at least 1 dose of the IMP. The ATS

consisted of all participants who received at least 1 dose of active treatment (BKZ or ADA) during the ATP (Week 16 and after).

End point type	Secondary

End point timeframe:

From Baseline until Safety Follow-Up (up to Week 72)

End point values	Placebo	Placebo/BKZ 160 mg Q4W	BKZ 160 mg Q4W	BKZ 160 mg Q4W/BKZ 160 mg Q4W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	281	271	431	414
Units: percentage of participants				
number (not applicable)	1.1	1.8	1.9	2.7

End point values	ADA 40 mg Q2W	ADA 40 mg Q2W/ADA 40 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	140	136		
Units: percentage of participants				
number (not applicable)	2.1	3.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with treatment-emergent adverse events (TEAEs) during the study

End point title	Percentage of Participants with treatment-emergent adverse events (TEAEs) during the study

End point description:

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE could therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. TEAEs were defined as any AEs with an onset date on or after the date of first IMP administration and within 140 days after the final dose of IMP. The Safety Set consisted of all participants who received at least 1 dose of the IMP. The ATS consisted of all participants who received at least 1 dose of active treatment (BKZ or ADA) during the ATP (Week 16 and after).

End point type	Secondary

End point timeframe:

From Baseline until Safety Follow-Up (up to Week 72)

End point values	Placebo	Placebo/BKZ 160 mg Q4W	BKZ 160 mg Q4W	BKZ 160 mg Q4W/BKZ 160 mg Q4W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	281	271	431	414
Units: percentage of participants				
number (not applicable)	49.5	70.5	59.6	72.0

End point values	ADA 40 mg Q2W	ADA 40 mg Q2W/ADA 40 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	140	136		
Units: percentage of participants				
number (not applicable)	59.3	68.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with treatment-emergent serious adverse events (SAEs) during the study

End point title	Percentage of Participants with treatment-emergent serious adverse events (SAEs) during the study

End point description:

A SAE is any untoward medical occurrence that at any dose: Results in death, is life-threatening, requires in patient hospitalization or prolongation of existing hospitalization; is a congenital anomaly or birth defect; is an infection that requires treatment parenteral antibiotics, other important medical events which based on medical or scientific judgement may jeopardize the patients, or may require medical or surgical intervention to prevent any of the above. TEAEs were defined as any AEs with an onset date on or after the date of first IMP administration and within 140 days after the final dose of IMP. The Safety Set consisted of all participants who received at least 1 dose of the IMP. The ATS consisted of all participants who received at least 1 dose of active treatment (BKZ or ADA) during the ATP (Week 16 and after).

End point type	Secondary

End point timeframe:

From Baseline until Safety Follow-Up (up to Week 72)

End point values	Placebo	Placebo/BKZ 160 mg Q4W	BKZ 160 mg Q4W	BKZ 160 mg Q4W/BKZ 160 mg Q4W
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	281	271	431	414
Units: percentage of participants				
number (not applicable)	1.1	5.9	1.9	5.6

End point values	ADA 40 mg Q2W	ADA 40 mg Q2W/ADA 40 mg Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	140	136		
Units: percentage of participants				
number (not applicable)	1.4	6.6		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline until Safety Follow-Up (up to Week 72)

Adverse event reporting additional description:

TEAEs were defined as any AEs with an onset date on or after the date of first IMP administration and within 140 days after the final dose of IMP. TEAEs were analyzed and reported for DBP (safety set) and ATP (ATS) separately.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received placebo during the 16-weeks Double-Blind Treatment Period (DBP).

Reporting group title	BKZ 160 mg Q4W

Reporting group description:

Participants received BKZ 160 milligrams (mg) subcutaneous (SC) every 4 weeks (Q4W) during the 16-weeks DBP.

Reporting group title	ADA 40 mg Q2W

Reporting group description:

Participants received ADA 40 mg SC every 2 weeks (Q2W) during the 16-weeks DBP.

Reporting group title	Placebo/BKZ 160 mg Q4W

Reporting group description:

After the 16-weeks DBP, participants initially randomized to placebo received BKZ 160 mg SC Q4W during the 36-weeks ATP.

Reporting group title	BKZ 160 mg Q4W/BKZ 160 mg Q4W

Reporting group description:

After the 16-weeks DBP, participants initially randomized to BKZ 160 mg continued to receive BKZ 160 mg SC Q4W during the 36-weeks ATP.

Reporting group title	ADA 40 mg Q2W/ADA 40 mg Q2W

Reporting group description:

After the 16-weeks DBP, participants initially randomized to ADA 40 mg continued to receive ADA 40 mg SC Q2W during the 36-weeks ATP.

Serious adverse events	Placebo	BKZ 160 mg Q4W	ADA 40 mg Q2W
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 281 (1.07%)	8 / 431 (1.86%)	2 / 140 (1.43%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer stage I			

subjects affected / exposed	1 / 281 (0.36%)	0 / 431 (0.00%)	0 / 140 (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
Enchondromatosis			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	0 / 281 (0.00%)	1 / 431 (0.23%)	0 / 140 (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
Chronic lymphocytic leukaemia stage 0			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Parathyroid tumour benign			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Colon cancer			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Papillary thyroid cancer			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Reproductive system and breast			

disorders			
Vaginal prolapse			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Cervical polyp			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Uterine inflammation			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Uterine haemorrhage			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Pneumothorax			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Hypertension			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Deep vein thrombosis			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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

Vascular disorders			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Asthma			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Anxiety			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 281 (0.00%)	1 / 431 (0.23%)	0 / 140 (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
Blood bilirubin increased			
subjects affected / exposed	0 / 281 (0.00%)	1 / 431 (0.23%)	0 / 140 (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
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	0 / 281 (0.00%)	1 / 431 (0.23%)	0 / 140 (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
Ankle fracture			

subjects affected / exposed	1 / 281 (0.36%)	0 / 431 (0.00%)	0 / 140 (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
Meniscus injury			
subjects affected / exposed	0 / 281 (0.00%)	1 / 431 (0.23%)	0 / 140 (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
Joint injury			
subjects affected / exposed	0 / 281 (0.00%)	1 / 431 (0.23%)	0 / 140 (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
Brain contusion			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Multiple fractures			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Hip fracture			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Radius fracture			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Traumatic shock			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Rib fracture			

subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Pubis fracture			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Road traffic accident			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	0 / 281 (0.00%)	1 / 431 (0.23%)	0 / 140 (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
Atrial fibrillation			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Myocardial ischaemia			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Myocardial infarction			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Coronary artery stenosis			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Nervous system disorders			

Cerebrovascular accident			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Thrombotic cerebral infarction			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Ischaemic stroke			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 281 (0.00%)	1 / 431 (0.23%)	0 / 140 (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
Proctitis			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Rectal haemorrhage			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Enteritis			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	0 / 281 (0.00%)	1 / 431 (0.23%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Non-alcoholic steatohepatitis			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Cholelithiasis			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Renal and urinary disorders			
IgA nephropathy			
subjects affected / exposed	1 / 281 (0.36%)	0 / 431 (0.00%)	0 / 140 (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
Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Goitre			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Musculoskeletal and connective tissue disorders			
Osteonecrosis			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Haemarthrosis			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Chondropathy			

subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Osteoarthritis			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Back pain			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Intervertebral disc protrusion			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Foot deformity			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Infections and infestations			
Herpes zoster			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 281 (0.00%)	1 / 431 (0.23%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Gangrene			

subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Otitis media			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Atypical pneumonia			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Upper respiratory tract infections			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Urinary tract infections			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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
Cystitis			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (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	Placebo/BKZ 160 mg Q4W	BKZ 160 mg Q4W/BKZ 160 mg Q4W	ADA 40 mg Q2W/ADA 40 mg Q2W
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 271 (5.90%)	23 / 414 (5.56%)	9 / 136 (6.62%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer stage I			

subjects affected / exposed	0 / 271 (0.00%)	0 / 414 (0.00%)	0 / 136 (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
Enchondromatosis			
subjects affected / exposed	0 / 271 (0.00%)	0 / 414 (0.00%)	0 / 136 (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
Basal cell carcinoma			
subjects affected / exposed	0 / 271 (0.00%)	0 / 414 (0.00%)	0 / 136 (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
Chronic lymphocytic leukaemia stage 0			
subjects affected / exposed	1 / 271 (0.37%)	0 / 414 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parathyroid tumour benign			
subjects affected / exposed	0 / 271 (0.00%)	1 / 414 (0.24%)	0 / 136 (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
Colon cancer			
subjects affected / exposed	1 / 271 (0.37%)	0 / 414 (0.00%)	0 / 136 (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
Papillary thyroid cancer			
subjects affected / exposed	1 / 271 (0.37%)	0 / 414 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 271 (0.00%)	1 / 414 (0.24%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast			

disorders			
Vaginal prolapse			
subjects affected / exposed	1 / 271 (0.37%)	0 / 414 (0.00%)	0 / 136 (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
Cervical polyp			
subjects affected / exposed	0 / 271 (0.00%)	1 / 414 (0.24%)	0 / 136 (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
Uterine inflammation			
subjects affected / exposed	0 / 271 (0.00%)	1 / 414 (0.24%)	0 / 136 (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
Uterine haemorrhage			
subjects affected / exposed	1 / 271 (0.37%)	0 / 414 (0.00%)	0 / 136 (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
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 271 (0.00%)	1 / 414 (0.24%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 271 (0.00%)	1 / 414 (0.24%)	0 / 136 (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
Hypertension			
subjects affected / exposed	0 / 271 (0.00%)	1 / 414 (0.24%)	0 / 136 (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
Deep vein thrombosis			
subjects affected / exposed	1 / 271 (0.37%)	0 / 414 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vascular disorders			
subjects affected / exposed	1 / 271 (0.37%)	1 / 414 (0.24%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	0 / 271 (0.00%)	0 / 414 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	0 / 271 (0.00%)	1 / 414 (0.24%)	0 / 136 (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
Anxiety			
subjects affected / exposed	1 / 271 (0.37%)	0 / 414 (0.00%)	0 / 136 (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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 271 (0.00%)	0 / 414 (0.00%)	0 / 136 (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
Blood bilirubin increased			
subjects affected / exposed	0 / 271 (0.00%)	0 / 414 (0.00%)	0 / 136 (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
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	0 / 271 (0.00%)	0 / 414 (0.00%)	0 / 136 (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
Ankle fracture			

subjects affected / exposed	0 / 271 (0.00%)	0 / 414 (0.00%)	0 / 136 (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
Meniscus injury			
subjects affected / exposed	0 / 271 (0.00%)	0 / 414 (0.00%)	0 / 136 (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
Joint injury			
subjects affected / exposed	0 / 271 (0.00%)	0 / 414 (0.00%)	0 / 136 (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
Brain contusion			
subjects affected / exposed	0 / 271 (0.00%)	1 / 414 (0.24%)	0 / 136 (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
Multiple fractures			
subjects affected / exposed	0 / 271 (0.00%)	1 / 414 (0.24%)	0 / 136 (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
Hip fracture			
subjects affected / exposed	0 / 271 (0.00%)	1 / 414 (0.24%)	0 / 136 (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
Radius fracture			
subjects affected / exposed	0 / 271 (0.00%)	0 / 414 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic shock			
subjects affected / exposed	1 / 271 (0.37%)	0 / 414 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Rib fracture			

subjects affected / exposed	0 / 271 (0.00%)	1 / 414 (0.24%)	0 / 136 (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
Pubis fracture			
subjects affected / exposed	0 / 271 (0.00%)	1 / 414 (0.24%)	0 / 136 (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
Road traffic accident			
subjects affected / exposed	1 / 271 (0.37%)	0 / 414 (0.00%)	0 / 136 (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
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	0 / 271 (0.00%)	0 / 414 (0.00%)	0 / 136 (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
Atrial fibrillation			
subjects affected / exposed	1 / 271 (0.37%)	1 / 414 (0.24%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 271 (0.00%)	1 / 414 (0.24%)	0 / 136 (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
Myocardial infarction			
subjects affected / exposed	0 / 271 (0.00%)	1 / 414 (0.24%)	0 / 136 (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
Coronary artery stenosis			
subjects affected / exposed	0 / 271 (0.00%)	1 / 414 (0.24%)	0 / 136 (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
Nervous system disorders			

Cerebrovascular accident			
subjects affected / exposed	1 / 271 (0.37%)	0 / 414 (0.00%)	0 / 136 (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
Thrombotic cerebral infarction			
subjects affected / exposed	0 / 271 (0.00%)	1 / 414 (0.24%)	0 / 136 (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
Ischaemic stroke			
subjects affected / exposed	0 / 271 (0.00%)	1 / 414 (0.24%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 271 (0.00%)	0 / 414 (0.00%)	0 / 136 (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
Proctitis			
subjects affected / exposed	1 / 271 (0.37%)	0 / 414 (0.00%)	0 / 136 (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
Rectal haemorrhage			
subjects affected / exposed	1 / 271 (0.37%)	0 / 414 (0.00%)	0 / 136 (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
Enteritis			
subjects affected / exposed	0 / 271 (0.00%)	1 / 414 (0.24%)	0 / 136 (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
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	0 / 271 (0.00%)	0 / 414 (0.00%)	0 / 136 (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

Non-alcoholic steatohepatitis			
subjects affected / exposed	0 / 271 (0.00%)	0 / 414 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 271 (0.37%)	1 / 414 (0.24%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
IgA nephropathy			
subjects affected / exposed	0 / 271 (0.00%)	0 / 414 (0.00%)	0 / 136 (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
Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	0 / 271 (0.00%)	1 / 414 (0.24%)	0 / 136 (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
Goitre			
subjects affected / exposed	0 / 271 (0.00%)	0 / 414 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteonecrosis			
subjects affected / exposed	0 / 271 (0.00%)	1 / 414 (0.24%)	0 / 136 (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
Haemarthrosis			
subjects affected / exposed	0 / 271 (0.00%)	0 / 414 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chondropathy			

subjects affected / exposed	0 / 271 (0.00%)	0 / 414 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 271 (0.00%)	2 / 414 (0.48%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 271 (0.00%)	1 / 414 (0.24%)	0 / 136 (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
Intervertebral disc protrusion			
subjects affected / exposed	0 / 271 (0.00%)	0 / 414 (0.00%)	2 / 136 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot deformity			
subjects affected / exposed	1 / 271 (0.37%)	0 / 414 (0.00%)	0 / 136 (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			
Herpes zoster			
subjects affected / exposed	0 / 271 (0.00%)	0 / 414 (0.00%)	0 / 136 (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
Pneumonia			
subjects affected / exposed	0 / 271 (0.00%)	0 / 414 (0.00%)	0 / 136 (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
Cellulitis			
subjects affected / exposed	0 / 271 (0.00%)	1 / 414 (0.24%)	0 / 136 (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
Gangrene			

subjects affected / exposed	0 / 271 (0.00%)	1 / 414 (0.24%)	0 / 136 (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
Otitis media			
subjects affected / exposed	0 / 271 (0.00%)	0 / 414 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical pneumonia			
subjects affected / exposed	0 / 271 (0.00%)	0 / 414 (0.00%)	1 / 136 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infections			
subjects affected / exposed	0 / 271 (0.00%)	1 / 414 (0.24%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infections			
subjects affected / exposed	1 / 271 (0.37%)	0 / 414 (0.00%)	0 / 136 (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
Cystitis			
subjects affected / exposed	1 / 271 (0.37%)	0 / 414 (0.00%)	0 / 136 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	BKZ 160 mg Q4W	ADA 40 mg Q2W
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 281 (11.03%)	62 / 431 (14.39%)	10 / 140 (7.14%)
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	13 / 281 (4.63%)	40 / 431 (9.28%)	7 / 140 (5.00%)
occurrences (all)	14	44	8
Urinary tract infection			

subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (0.00%)
occurrences (all)	0	0	0
Oral candidiasis			
subjects affected / exposed	0 / 281 (0.00%)	0 / 431 (0.00%)	0 / 140 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	18 / 281 (6.41%)	22 / 431 (5.10%)	3 / 140 (2.14%)
occurrences (all)	18	25	3

Non-serious adverse events	Placebo/BKZ 160 mg Q4W	BKZ 160 mg Q4W/BKZ 160 mg Q4W	ADA 40 mg Q2W/ADA 40 mg Q2W
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 271 (16.97%)	66 / 414 (15.94%)	10 / 136 (7.35%)
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	23 / 271 (8.49%)	29 / 414 (7.00%)	6 / 136 (4.41%)
occurrences (all)	28	31	7
Urinary tract infection			
subjects affected / exposed	15 / 271 (5.54%)	20 / 414 (4.83%)	3 / 136 (2.21%)
occurrences (all)	17	20	6
Oral candidiasis			
subjects affected / exposed	14 / 271 (5.17%)	19 / 414 (4.59%)	1 / 136 (0.74%)
occurrences (all)	14	26	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 271 (0.00%)	0 / 414 (0.00%)	0 / 136 (0.00%)
occurrences (all)	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 January 2020	Protocol Amendment 1 (10 Jan 2020) was implemented to update the completed and ongoing studies information, clarify study procedures, update the description of the IMP, and to apply a minimum percentage for enrollment of study participants who had elevated hs-CRP and/or have at least 1 bone erosion at Screening.
22 February 2021	Protocol Amendment 2 (22 Feb 2021) was implemented to modify the secondary variables and fixed sequence testing procedure, update the statistical section, and make other procedural clarifications.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported