Clinical trial results:
KPL-716-C201: A Phase 2a/b, Randomized, Double-Blind, Placebo Controlled Study to Investigate the Efficacy, Safety, Tolerability and Pharmacokinetics of KPL-716 in Reducing Pruritus in Subjects with Prurigo Nodularis

Summary

EudraCT number	2020-004198-38
Trial protocol	CZ DE FR BE IT AT
Global end of trial date	24 August 2023

Results information

Result version number	v1 (current)
This version publication date	07 July 2024
First version publication date	07 July 2024

Trial information

Trial identification

Sponsor protocol code	KPL-716-C201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03816891
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 132912

Notes:

Sponsors

Sponsor organisation name	Kiniksa Pharmaceuticals, Ltd
Sponsor organisation address	100 Hayden Avenue, Lexington, Massachusetts, United States, 02421
Public contact	Chrissy Lundquist, Kiniksa Pharmaceuticals, Ltd. , +1 7813170276, clundquist@kiniksa.com
Scientific contact	Chrissy Lundquist, Kiniksa Pharmaceuticals, Ltd. , +1 7813170276, clundquist@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	26 March 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 December 2022
Global end of trial reached?	Yes
Global end of trial date	24 August 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of subcutaneous (SC) KPL-716 vs. placebo in reducing pruritus in Prurigo Nodularis (PN) subjects experiencing severe pruritus

Protection of trial subjects:

(1) Independent Ethics Committee (IEC) or Institutional Review Board (IRB): The core study documents (Protocol and subsequent amendments, Investigator's Brochure (IB), Patient facing materials [Informed Consent Form (ICF), Subject recruitment procedures (e.g. advertisements), any other written information provided to subjects] were reviewed and approved by the IRB/ IEC before implementation. Additionally, the IRBs/IECs were informed by the Investigator of serious and unexpected SAEs in accordance with the reporting requirements.

(2) Ethical Conduct: The study was conducted (a) in accordance with the protocol (b) per consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines (c) per applicable International Council for/Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines (d) per applicable country and local laws and regulations.

(3) ICF: The investigator or their representative explained the nature of the study to the participants or their legally authorized representative before signing the ICF. Participants were re-consented to the most current version of the ICF(s) during their participation in the study. A copy of the ICF(s) was provided to the participant or the participant’s legally authorized representative.

Background therapy:

There are no approved therapies for PN. Topical therapies such as topical corticosteroids, calcineurin inhibitors, calcipotriol, and capsaicin, systemic corticosteroids, thalidomide, systemic immunomodulatory drugs such as methotrexate and cyclosporin, antiepileptics and antidepressants, phototherapy and photochemotherapy are often tried with limited success.

Evidence for comparator:

-

Actual start date of recruitment	01 December 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 7
Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Czechia: 4
Country: Number of subjects enrolled	France: 3

Country: Number of subjects enrolled	Germany: 28
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	United States: 72
Country: Number of subjects enrolled	Canada: 28
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	Korea, Republic of: 6
Country: Number of subjects enrolled	Taiwan: 16
Worldwide total number of subjects	190
EEA total number of subjects	57

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)	137
From 65 to 84 years	53
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 443 participants were screened and 190 participants enrolled subjects were randomized at 1:1:1:1 ratio into one of the 4 arms to receive different dosing regimens of or placebo. At the end of the Double-Blind Period, all participants had the option to enter the Open Label Extension Period to receive KPL-716.

Pre-assignment

Screening details:

After ICF was signed, 443 participants entered the Screening Period for assessment of eligibility. A full physical examination was performed to assess the following systems: head/neck/thyroid; eyes/ears/nose/throat (EENT); respiratory; cardiovascular; lymph nodes; abdomen; skin; musculoskeletal; and neurological.

Period 1

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

Blinding implementation details:

An Interact Web Response System issued a unique treatment code to each subject, which assigned the treatment for the subject. The investigator, the sponsor study team, and remaining clinical site staff (other than the unblinded pharmacist or unblinded designee) were blinded to treatment assignment. The unblinded treatment assignment for individual participant was made available to the investigator only in the event of a medical emergency or or an adverse reaction.

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

KPL-716 was administered subcutaneously at the dose of 540 mg every 4 weeks for 16 weeks during double blind period.

Arm type	Experimental
Investigational medicinal product name	KPL-716
Investigational medicinal product code	
Other name	Vixarelimab
Pharmaceutical forms	Injection/infusion
Routes of administration	Cutaneous use

Dosage and administration details:

KPL-716 is provided as a sterile liquid formulation and supplied as a single-use vial for SC injection.

Arm title	Arm B

Arm description:

KPL-716 was administered subcutaneously at the dose of 360 mg every 4 weeks for 16 weeks during the double-blind period.

Arm type	Experimental
Investigational medicinal product name	KPL-716
Investigational medicinal product code	
Other name	Vixarelimab
Pharmaceutical forms	Injection/infusion
Routes of administration	Cutaneous use

Dosage and administration details:

KPL-716 is provided as a sterile liquid formulation and supplied as a single-use vial for SC injection.

Arm title	Arm C

Arm description:

KPL-716 was administered subcutaneously at the dose of 120 mg every 4 weeks for 16 weeks during double blind period.

Arm type	Experimental
Investigational medicinal product name	KPL-716
Investigational medicinal product code	
Other name	Vixarelimab
Pharmaceutical forms	Injection/infusion
Routes of administration	Cutaneous use

Dosage and administration details:

KPL-716 was provided as a sterile liquid formulation and supplied as a single-use vial for SC injection.

Arm title	Arm D

Arm description:

Placebo was administered subcutaneously every 4 weeks for 16 weeks during the double-blind period.

Arm type	Placebo
Investigational medicinal product name	Matching Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Cutaneous use

Dosage and administration details:

Placebo matching to KPL-716 excipients was provided as a sterile liquid formulation and supplied for SC injection

Number of subjects in period 1	Arm A	Arm B	Arm C
Started	47	47	47
Completed	45	44	47
Not completed	2	3	0
Physician decision	-	1	-
Consent withdrawn by subject	-	1	-
Adverse event, non-fatal	2	1	-
Lost to follow-up	-	-	-
Early discontinuation	-	-	-

Number of subjects in period 1	Arm D
Started	49
Completed	47
Not completed	2
Physician decision	-
Consent withdrawn by subject	-
Adverse event, non-fatal	-
Lost to follow-up	1
Early discontinuation	1

Period 2

Period 2 title	Open Label Extension
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Treatment

Arm description:

Open label extension participants who previously received KPL-716 during Double-Blind period. KPL-716 was administered subcutaneously at the dose of 360 mg every 2 weeks for 36 weeks (starting at week 16 and with the last dosing at the week 48 visit).

Arm type	Experimental
Investigational medicinal product name	KPL-716
Investigational medicinal product code	
Other name	Vixarelimab
Pharmaceutical forms	Injection/infusion
Routes of administration	Cutaneous use

Dosage and administration details:

KPL-716 is provided as a sterile liquid formulation and supplied as a single-use vial for SC injection.

Number of subjects in period 2[1]	Treatment
Started	181
Completed	157
Not completed	24
Consent withdrawn by subject	9
Adverse event, non-fatal	8
Lost to follow-up	3
Lack of efficacy	4

Notes:

[1] - 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: Per study design, all subjects in doble blind period (DB) had an option of receive KPL-716 360 mg SC,
Q2W during the Open Label Extension (OLE) Period to evaluate the long-term safety and PK. Out of 190

subjects randomized in DB period, 181 consented to OLE.

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description:	
KPL-716 was administered subcutaneously at the dose of 540 mg every 4 weeks for 16 weeks during double blind period.	
Reporting group title	Arm B
Reporting group description:	
KPL-716 was administered subcutaneously at the dose of 360 mg every 4 weeks for 16 weeks during the double-blind period.	
Reporting group title	Arm C
Reporting group description:	
KPL-716 was administered subcutaneously at the dose of 120 mg every 4 weeks for 16 weeks during double blind period.	
Reporting group title	Arm D
Reporting group description:	
Placebo was administered subcutaneously every 4 weeks for 16 weeks during the double-blind period.	

Reporting group values	Arm A	Arm B	Arm C
Number of subjects	47	47	47
Age categorical			
KPL-716 was administered subcutaneously at the dose of 360 mg every 2 weeks for 36 weeks (starting at week 16 and with the last dosing at the week 48 visit).			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	31	35	35
From 65-84 years	16	12	12
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	56.7	55.9	54.4
standard deviation	± 12.18	± 13.73	± 16.11
Gender categorical			
Units: Subjects			
Female	29	28	28
Male	18	19	19

Reporting group values	Arm D	Total	
Number of subjects	49	190	
Age categorical			
KPL-716 was administered subcutaneously at the dose of 360 mg every 2 weeks for 36 weeks (starting at week 16 and with the last dosing at the week 48 visit).			
Units: Subjects			

In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	36	137	
From 65-84 years	13	53	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	54.8		
standard deviation	± 13.35	-	
Gender categorical			
Units: Subjects			
Female	29	114	
Male	20	76	

Subject analysis sets

Subject analysis set title	mITT efficacy analysis
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All randomized subjects who receive at least 1 dose of KPL-716 or placebo and have at least 1 post-baseline efficacy assessment in the double-blind treatment period were included in the modified intent-to-treat (mITT) analysis set.

Reporting group values	mITT efficacy analysis		
Number of subjects	189		
Age categorical			
KPL-716 was administered subcutaneously at the dose of 360 mg every 2 weeks for 36 weeks (starting at week 16 and with the last dosing at the week 48 visit).			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	136		
From 65-84 years	53		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	55.4		
standard deviation	± 13.83		
Gender categorical			
Units: Subjects			
Female	114		

Male	75		

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description:	
KPL-716 was administered subcutaneously at the dose of 540 mg every 4 weeks for 16 weeks during double blind period.	
Reporting group title	Arm B
Reporting group description:	
KPL-716 was administered subcutaneously at the dose of 360 mg every 4 weeks for 16 weeks during the double-blind period.	
Reporting group title	Arm C
Reporting group description:	
KPL-716 was administered subcutaneously at the dose of 120 mg every 4 weeks for 16 weeks during double blind period.	
Reporting group title	Arm D
Reporting group description:	
Placebo was administered subcutaneously every 4 weeks for 16 weeks during the double-blind period.	
Reporting group title	Treatment
Reporting group description:	
Open label extension participants who previously received KPL-716 during Double-Blind period. KPL-716 was administered subcutaneously at the dose of 360 mg every 2 weeks for 36 weeks (starting at week 16 and with the last dosing at the week 48 visit).	

Subject analysis set title	mITT efficacy analysis
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized subjects who receive at least 1 dose of KPL-716 or placebo and have at least 1 post-baseline efficacy assessment in the double-blind treatment period were included in the modified intent-to-treat (mITT) analysis set.	

Primary: 1. Percent change from baseline in weekly average Worst Itch–Numeric Rating Scale (WI-NRS) at Week 16

End point title	1. Percent change from baseline in weekly average Worst Itch–Numeric Rating Scale (WI-NRS) at Week 16
End point description:	
All efficacy analyses were performed in the mITT analysis set.	
End point type	Primary
End point timeframe:	
Percent change from baseline in weekly average WI-NRS was measured at week 16 using mITT analysis set	

End point values	Arm A	Arm B	Arm C	Arm D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45	45	47	47
Units: Score				
arithmetic mean (standard deviation)	-56.2 (± 35.7)	-51.2 (± 31.91)	-33 (± 34.31)	-14.8 (± 25.86)

Statistical analyses

Statistical analysis title	Analysis of covariance

Statistical analysis description:

The primary efficacy endpoint (percentage change from baseline of WI-NRS at Week 16) was analyzed with ANCOVA with treatment and randomization stratification factors of sex and years since the first nodule observed (i.e., ≥10 versus <10 years) as fixed effect factors, baseline as covariates.

Comparison groups	Arm A v Arm D
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Statistical analysis title	Analysis of covariance

Statistical analysis description:

The primary efficacy endpoint (percentage change from baseline of WI-NRS at Week 16) was analyzed with ANCOVA with treatment and randomization stratification factors of sex and years since the first nodule observed (i.e., ≥10 versus <10 years) as fixed effect factors, baseline as covariates

Comparison groups	Arm B v Arm D
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Statistical analysis title	Analysis of covariance

Statistical analysis description:

The primary efficacy endpoint (percentage change from baseline of WI-NRS at Week 16) was analyzed with ANCOVA with treatment and randomization stratification factors of sex and years since the first nodule observed (i.e., ≥10 versus <10 years) as fixed effect factors, baseline as covariates.

Comparison groups	Arm C v Arm D
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0061
Method	ANCOVA

Secondary: 2.1 Proportion of subjects achieving at least a 6-point reduction from baseline in weekly average WI-NRS at Week 16

End point title	2.1 Proportion of subjects achieving at least a 6-point reduction from baseline in weekly average WI-NRS at Week 16

End point description:

All efficacy analyses were performed in the mITT analysis set.

End point type	Secondary

End point timeframe:

Baseline up to week 16

End point values	Arm A	Arm B	Arm C	Arm D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	47	47	46	48
Units: Percentage				
number (confidence interval 95%)	42.6 (28.3 to 57.8)	23.4 (12.3 to 38)	17.4 (7.8 to 31.4)	2.1 (0.1 to 11.1)

Statistical analyses

No statistical analyses for this end point

Secondary: 2.2 Proportion of subjects achieving at least a 4-point reduction from baseline in weekly average WI-NRS at Week 16

End point title	2.2 Proportion of subjects achieving at least a 4-point reduction from baseline in weekly average WI-NRS at Week 16

End point description:

End point type	Secondary

End point timeframe:

Baseline up to week 16

End point values	Arm A	Arm B	Arm C	Arm D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	47	47	47	48
Units: Percentage				
number (confidence interval 95%)	66 (50.7 to 79.1)	61.7 (46.4 to 75.5)	29.8 (17.3 to 44.9)	16.7 (7.5 to 30.2)

Statistical analyses

No statistical analyses for this end point

Secondary: 2.3 Proportion of subjects achieving 0 or 1 in Prurigo Nodularis - Investigator Global Assessment at week 16

End point title	2.3 Proportion of subjects achieving 0 or 1 in Prurigo Nodularis - Investigator Global Assessment at week 16

End point description:

Proportion of subjects achieving clear (0) or almost Clear (1) in PN-IGA score at week 16 (mITT Analysis Set)

End point type	Secondary

End point timeframe:

At week 16

End point values	Arm A	Arm B	Arm C	Arm D
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	47	47	47	48
Units: Percentage				
number (confidence interval 95%)	38.3 (24.5 to 53.6)	29.8 (17.3 to 44.9)	14.9 (6.2 to 28.3)	10.4 (3.5 to 22.7)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were observed or reported during the study from the time the subject signs the ICF through the EOS Visit. Serious Adverse Event and Adverse Event of Special Interest were reported to the Sponsor or designee within 24 hours of occurrence.

Adverse event reporting additional description:

Data presented here reports Treatment-Emergent Adverse Events of Any Grade Occurring in ≥ 5% of the Subjects During the Double-Blind and Open-Label Extension Period (Safety Analysis Set)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Double Blind-Arm A

Reporting group description:

KPL-716 was administered subcutaneously at the dose of 540 mg every 4 weeks for 16 weeks during double blind period.

Reporting group title	Double Blind-Arm B

Reporting group description:

KPL-716 was administered subcutaneously at the dose of 360 mg every 4 weeks for 16 weeks during the double-blind period.

Reporting group title	Double Blind-Arm C

Reporting group description:

KPL-716 was administered subcutaneously at the dose of 120 mg every 4 weeks for 16 weeks during double blind period.

Reporting group title	Double Blind-Arm D

Reporting group description:

Placebo was administered subcutaneously every 4 weeks during the double-blind period.

Reporting group title	Open-Label Extension Period

Reporting group description:

Data presented here reports Treatment-Related Adverse Events of Any Grade Occurring in ≥ 5% of the Subjects During the Open-Label Extension Period (Safety Analysis Set)

Serious adverse events	Double Blind-Arm A	Double Blind-Arm B	Double Blind-Arm C
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 47 (6.38%)	0 / 47 (0.00%)	1 / 47 (2.13%)
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)			
Colon cancer			
subjects affected / exposed	0 / 47 (0.00%)	0 / 47 (0.00%)	0 / 47 (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			
Humerus fracture			
subjects affected / exposed	0 / 47 (0.00%)	0 / 47 (0.00%)	0 / 47 (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
Spinal fusion fracture			
subjects affected / exposed	0 / 47 (0.00%)	0 / 47 (0.00%)	0 / 47 (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			
Supraventricular extrasystoles			
subjects affected / exposed	0 / 47 (0.00%)	0 / 47 (0.00%)	0 / 47 (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			
Syncope			
subjects affected / exposed	0 / 47 (0.00%)	0 / 47 (0.00%)	0 / 47 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 47 (0.00%)	0 / 47 (0.00%)	0 / 47 (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
Facial Paralysis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 47 (0.00%)	0 / 47 (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			
Small intestinal obstruction			
subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	0 / 47 (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
Ileus			

subjects affected / exposed	0 / 47 (0.00%)	0 / 47 (0.00%)	0 / 47 (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 Ulcer			
subjects affected / exposed	0 / 47 (0.00%)	0 / 47 (0.00%)	0 / 47 (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			
Cholelithiasis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 47 (0.00%)	1 / 47 (2.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Eczema nummular			
subjects affected / exposed	0 / 47 (0.00%)	0 / 47 (0.00%)	0 / 47 (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			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	0 / 47 (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
Infections and infestations			
Periorbital cellulitis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	0 / 47 (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

Serious adverse events	Double Blind-Arm D	Open-Label Extension Period	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 48 (6.25%)	8 / 181 (4.42%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Colon cancer			
subjects affected / exposed	1 / 48 (2.08%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	0 / 48 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fusion fracture			
subjects affected / exposed	0 / 48 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Supraventricular extrasystoles			
subjects affected / exposed	0 / 48 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 48 (2.08%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 48 (2.08%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial Paralysis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Small intestinal obstruction			

subjects affected / exposed	0 / 48 (0.00%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 48 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal Ulcer			
subjects affected / exposed	0 / 48 (0.00%)	1 / 181 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Eczema nummular			
subjects affected / exposed	0 / 48 (0.00%)	2 / 181 (1.10%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 48 (0.00%)	0 / 181 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Periorbital cellulitis			
subjects affected / exposed	0 / 48 (0.00%)	0 / 181 (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	Double Blind-Arm A	Double Blind-Arm B	Double Blind-Arm C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 47 (74.47%)	29 / 47 (61.70%)	21 / 47 (44.68%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	1 / 47 (2.13%)
occurrences (all)	1	0	1
Vascular disorders			
Vascular disorders			
subjects affected / exposed	3 / 47 (6.38%)	0 / 47 (0.00%)	2 / 47 (4.26%)
occurrences (all)	3	0	2
General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed	7 / 47 (14.89%)	7 / 47 (14.89%)	4 / 47 (8.51%)
occurrences (all)	7	7	4
Immune system disorders			
Immune system disorders			
subjects affected / exposed	2 / 47 (4.26%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences (all)	2	0	0
Reproductive system and breast disorders			
Reproductive system and breast disorders			
subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	1 / 47 (2.13%)
occurrences (all)	1	0	1
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	1 / 47 (2.13%)	2 / 47 (4.26%)	2 / 47 (4.26%)
occurrences (all)	1	2	2
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	1 / 47 (2.13%)	1 / 47 (2.13%)	1 / 47 (2.13%)
occurrences (all)	1	1	1
Investigations			
Investigations			
subjects affected / exposed	4 / 47 (8.51%)	5 / 47 (10.64%)	3 / 47 (6.38%)
occurrences (all)	4	5	3

Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			
subjects affected / exposed	6 / 47 (12.77%)	4 / 47 (8.51%)	5 / 47 (10.64%)
occurrences (all)	6	4	5
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	0 / 47 (0.00%)	0 / 47 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
Nervous system disorders			
Nervous system disorders			
subjects affected / exposed	7 / 47 (14.89%)	3 / 47 (6.38%)	5 / 47 (10.64%)
occurrences (all)	7	3	5
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	1 / 47 (2.13%)	0 / 47 (0.00%)	1 / 47 (2.13%)
occurrences (all)	1	0	1
Ear and labyrinth disorders			
Ear and labyrinth disorders			
subjects affected / exposed	0 / 47 (0.00%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Eye disorders			
subjects affected / exposed	4 / 47 (8.51%)	1 / 47 (2.13%)	0 / 47 (0.00%)
occurrences (all)	4	1	0
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	6 / 47 (12.77%)	5 / 47 (10.64%)	5 / 47 (10.64%)
occurrences (all)	6	5	5
Hepatobiliary disorders			
Hepatobiliary disorders			
subjects affected / exposed	0 / 47 (0.00%)	0 / 47 (0.00%)	1 / 47 (2.13%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders			
subjects affected / exposed	10 / 47 (21.28%)	13 / 47 (27.66%)	5 / 47 (10.64%)
occurrences (all)	10	13	5
Renal and urinary disorders			

Renal and urinary disorders			
subjects affected / exposed	0 / 47 (0.00%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Endocrine disorders			
subjects affected / exposed	0 / 47 (0.00%)	0 / 47 (0.00%)	0 / 47 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders			
subjects affected / exposed	3 / 47 (6.38%)	1 / 47 (2.13%)	0 / 47 (0.00%)
occurrences (all)	3	1	0
Infections and infestations			
Infections and infestations			
subjects affected / exposed	14 / 47 (29.79%)	11 / 47 (23.40%)	11 / 47 (23.40%)
occurrences (all)	14	11	11
Metabolism and nutrition disorders			
Metabolism and nutrition disorders			
subjects affected / exposed	1 / 47 (2.13%)	4 / 47 (8.51%)	0 / 47 (0.00%)
occurrences (all)	1	4	0

Non-serious adverse events	Double Blind-Arm D	Open-Label Extension Period	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 48 (54.17%)	135 / 181 (74.59%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
subjects affected / exposed	0 / 48 (0.00%)	1 / 181 (0.55%)	
occurrences (all)	0	1	
Vascular disorders			
Vascular disorders			
subjects affected / exposed	4 / 48 (8.33%)	9 / 181 (4.97%)	
occurrences (all)	4	9	
General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed	7 / 48 (14.58%)	17 / 181 (9.39%)	
occurrences (all)	7	17	
Immune system disorders			

Immune system disorders			
subjects affected / exposed	0 / 48 (0.00%)	1 / 181 (0.55%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Reproductive system and breast disorders			
subjects affected / exposed	0 / 48 (0.00%)	1 / 181 (0.55%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	2 / 48 (4.17%)	16 / 181 (8.84%)	
occurrences (all)	2	16	
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	3 / 48 (6.25%)	8 / 181 (4.42%)	
occurrences (all)	3	8	
Investigations			
Investigations			
subjects affected / exposed	4 / 48 (8.33%)	18 / 181 (9.94%)	
occurrences (all)	4	18	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			
subjects affected / exposed	3 / 48 (6.25%)	15 / 181 (8.29%)	
occurrences (all)	3	15	
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	0 / 48 (0.00%)	1 / 181 (0.55%)	
occurrences (all)	0	1	
Nervous system disorders			
Nervous system disorders			
subjects affected / exposed	0 / 48 (0.00%)	13 / 181 (7.18%)	
occurrences (all)	0	13	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	0 / 48 (0.00%)	5 / 181 (2.76%)	
occurrences (all)	0	5	

Ear and labyrinth disorders Ear and labyrinth disorders subjects affected / exposed occurrences (all)	 1 / 48 (2.08%) 1	 3 / 181 (1.66%) 3	
Eye disorders Eye disorders subjects affected / exposed occurrences (all)	 0 / 48 (0.00%) 0	 5 / 181 (2.76%) 5	
Gastrointestinal disorders Gastrointestinal disorders subjects affected / exposed occurrences (all)	 4 / 48 (8.33%) 4	 22 / 181 (12.15%) 22	
Hepatobiliary disorders Hepatobiliary disorders subjects affected / exposed occurrences (all)	 1 / 48 (2.08%) 1	 1 / 181 (0.55%) 1	
Skin and subcutaneous tissue disorders Skin and subcutaneous tissue disorders subjects affected / exposed occurrences (all)	 3 / 48 (6.25%) 3	 49 / 181 (27.07%) 49	
Renal and urinary disorders Renal and urinary disorders subjects affected / exposed occurrences (all)	 1 / 48 (2.08%) 1	 2 / 181 (1.10%) 2	
Endocrine disorders Endocrine disorders subjects affected / exposed occurrences (all)	 1 / 48 (2.08%) 1	 1 / 181 (0.55%) 1	
Musculoskeletal and connective tissue disorders Musculoskeletal and connective tissue disorders subjects affected / exposed occurrences (all)	 0 / 48 (0.00%) 0	 25 / 181 (13.81%) 25	
Infections and infestations Infections and infestations subjects affected / exposed occurrences (all)	 14 / 48 (29.17%) 14	 87 / 181 (48.07%) 87	
Metabolism and nutrition disorders			

Metabolism and nutrition disorders subjects affected / exposed occurrences (all)	3 / 48 (6.25%) 3	11 / 181 (6.08%) 11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 August 2021	EU specific Protocol Amendment v1.0_06Aug2021: Global Protocol v5.0, dated 21 December 2020, was updated to a European Union Regional Protocol, v1.0, dated 06 August 2021, to incorporate comments and changes requested by European Regulatory Authorities during the initial clinical trial application review process. In summary the following important updates were made: (1) Clarified that the PN-IGA measures the overall assessment at Week 16 (2) Clarifications on sexually active female subjects, methods of contraception, and pregnancy test sections were included (3) Exclusion criteria were revised to reduce screen failures (4) Subject withdrawal and replacement section was updated per Germany regulatory authority (5) A new subsection "Suspected Unexpected Serious Adverse Reactions" was added to Safety and Tolerability Assessments.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None

Notes: