



Clinical trial results:

Multi-center, double-blind, randomised, placebo-controlled, phase IIa study to investigate efficacy, safety, tolerability, pharmacokinetics and pharmacogenomics of multiple intravenous doses of BI 655130 in patients with Palmoplantar Pustulosis (PPP)

Summary

EudraCT number	2016-004573-40
Trial protocol	SE DK ES DE IT
Global end of trial date	14 November 2018

Results information

Result version number	v1 (current)
This version publication date	11 November 2019
First version publication date	11 November 2019

Trial information

Trial identification

Sponsor protocol code	1368-0015
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03135548
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.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	17 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 July 2018
Global end of trial reached?	Yes
Global end of trial date	14 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial was to investigate the safety and efficacy of BI 655130 in patients with PPP following multiple intravenous administrations of either low dose or high dose of BI 655130 compared with placebo.

Protection of trial subjects:

Only patients that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All patients were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all patients was adhered to throughout the trial conduct. Rescue medication was allowed for all patients as required.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 June 2017
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	Denmark: 13
Country: Number of subjects enrolled	Canada: 19
Country: Number of subjects enrolled	Germany: 34
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Sweden: 3
Worldwide total number of subjects	79
EEA total number of subjects	60

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)	78
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a randomised, double-blind, placebo-controlled, parallel-design trial to investigate the safety and efficacy of BI 655130 in patients with Palmoplantar Pustulosis (PPP) following multiple intravenous administrations of either low dose or high dose compared with placebo.

Pre-assignment

Screening details:

All participants were screened for eligibility to participate in the trial. Participants attended specialist sites which would then ensure that all participants met all inclusion/exclusion criteria. Participants were not to be randomised to trial treatment if any one of the specific entry criteria were not met.

Period 1

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

Blinding implementation details:

This was a double-blind trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	BI 655130 low dose

Arm description:

Participants were administered low dose BI 655130 solution for infusion intravenously every 4 weeks at Day 1, 29, 57 and 85 until 12 weeks.

Arm type	Experimental
Investigational medicinal product name	BI 655130
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

low dose of BI 655130 solution for infusion intravenously every 4 weeks at Day 1, 29, 57 and 85 until 12 weeks

Arm title	BI 655130 high dose
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Arm description:

Participants were administered high dose BI 655130 solution for infusion intravenously every 4 weeks at Day 1, 29, 57 and 85 until 12 weeks.

Arm type	Experimental
Investigational medicinal product name	BI 655130
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

high dose of BI 655130 solution for infusion intravenously every 4 weeks at Day 1, 29, 57 and 85 until 12 weeks

Arm title	Placebo matching to BI 655130
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Arm description:

Participants were administered placebo matching to BI 655130 solution for infusion intravenously every

4 weeks at Day 1, 29, 57 and 85 until 12 weeks.

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

Dosage and administration details:

placebo matching to BI 655130 solution for infusion intravenously every 4 weeks at Day 1, 29, 57 and 85 until 12 weeks

Number of subjects in period 1^[1]	BI 655130 low dose	BI 655130 high dose	Placebo matching to BI 655130
Started	19	19	21
Completed	14	15	18
Not completed	5	4	3
Consent withdrawn by subject	2	2	1
Lost to follow-up	3	-	-
Other than listed	-	2	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Baseline characteristics are based on patients who were randomized after successfully completing the screening period and received at least one dose of the trial medication.

Baseline characteristics

Reporting groups

Reporting group title	BI 655130 low dose
Reporting group description:	
Participants were administered low dose BI 655130 solution for infusion intravenously every 4 weeks at Day 1, 29, 57 and 85 until 12 weeks.	
Reporting group title	BI 655130 high dose
Reporting group description:	
Participants were administered high dose BI 655130 solution for infusion intravenously every 4 weeks at Day 1, 29, 57 and 85 until 12 weeks.	
Reporting group title	Placebo matching to BI 655130
Reporting group description:	
Participants were administered placebo matching to BI 655130 solution for infusion intravenously every 4 weeks at Day 1, 29, 57 and 85 until 12 weeks.	

Reporting group values	BI 655130 low dose	BI 655130 high dose	Placebo matching to BI 655130
Number of subjects	19	19	21
Age categorical			
Units: Subjects			

Age Continuous			
Safety analysis set (SAF): SAF included all randomised patients who received at least one dose of study drug.			
Units: years			
arithmetic mean	54.6	49.4	46.3
standard deviation	± 7.7	± 11.3	± 11.7
Sex: Female, Male			
SAF			
Units: Subjects			
Female	16	16	17
Male	3	3	4
Race (NIH/OMB)			
SAF			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	1
White	18	19	19
More than one race	1	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
SAF			
Units: Subjects			
Hispanic or Latino	2	3	1
Not Hispanic or Latino	17	16	20
Unknown or Not Reported	0	0	0

Reporting group values	Total		
Number of subjects	59		
Age categorical			
Units: Subjects			
Age Continuous			
Safety analysis set (SAF): SAF included all randomised patients who received at least one dose of study drug.			
Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
SAF			
Units: Subjects			
Female	49		
Male	10		
Race (NIH/OMB)			
SAF			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	1		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	1		
White	56		
More than one race	1		
Unknown or Not Reported	0		
Ethnicity (NIH/OMB)			
SAF			
Units: Subjects			
Hispanic or Latino	6		
Not Hispanic or Latino	53		
Unknown or Not Reported	0		

End points

End points reporting groups

Reporting group title	BI 655130 low dose
Reporting group description: Participants were administered low dose BI 655130 solution for infusion intravenously every 4 weeks at Day 1, 29, 57 and 85 until 12 weeks.	
Reporting group title	BI 655130 high dose
Reporting group description: Participants were administered high dose BI 655130 solution for infusion intravenously every 4 weeks at Day 1, 29, 57 and 85 until 12 weeks.	
Reporting group title	Placebo matching to BI 655130
Reporting group description: Participants were administered placebo matching to BI 655130 solution for infusion intravenously every 4 weeks at Day 1, 29, 57 and 85 until 12 weeks.	

Primary: Percentage of participants with palmoplantar Pustular Psoriasis Area and Severity Index 50 (PPPASI50) at week 16

End point title	Percentage of participants with palmoplantar Pustular Psoriasis Area and Severity Index 50 (PPPASI50) at week 16
End point description: ppPASI is modification of PASI score and investigator assessment of extent and severity of pustular and plaque lesions on the palms and soles presenting in PPP participants. This tool provides numeric scoring for participants overall PPP disease state, ranging from 0 to maximum 72, where 0 corresponds to no signs of psoriasis. It is a linear combination of the percent of surface area of skin that is affected on the palms and soles and the severity of Erythema(E), Pustules(P)(total), and scaling(Desquamation(D)). Missing values for severity or area of involvement were not imputed. ppPASI was calculated as a weighted sum of the scores obtained for E,P,D and Area affected(%) (where area assessed is glabrous skin on palms/soles)(A): $[(E+P+D) \times A \times 0.2(\text{right palm})] + [(E+P+D) \times A \times 0.2(\text{left palm})] + [(E+P+D) \times A \times 0.3(\text{right sole})] + [(E+P+D) \times A \times 0.3(\text{left sole})]$. Full analysis set included all patients in the SAF who had a baseline measurement available for primary endpoint, with no response	
End point type	Primary
End point timeframe: Week 16	

End point values	BI 655130 low dose	BI 655130 high dose	Placebo matching to BI 655130	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19 ^[1]	19 ^[2]	21 ^[3]	
Units: Percentage of participants (%)				
number (not applicable)	31.6	31.6	23.8	

Notes:

[1] - FAS (NRI)

[2] - FAS (NRI)

[3] - FAS (NRI)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
95% confidence intervals (CI) are calculated using the method of Wilson/Newcombe. Unadjusted absolute risk difference versus placebo was calculated as the difference in the observed proportion of patients with ppPASI50 at Week 16 for each treatment scenario, for the FAS.	
Comparison groups	BI 655130 low dose v Placebo matching to BI 655130
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other ^[4]
Method	Wilson/Newcombe
Parameter estimate	Risk difference (RD)
Point estimate	0.078
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	0.338

Notes:

[4] - No formal hypothesis testing was performed in this trial.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
95% CIs are calculated using the method of Wilson/Newcombe. Unadjusted absolute risk difference versus placebo was calculated as the difference in the observed proportion of patients with ppPASI50 at Week 16 for each treatment scenario, for the FAS.	
Comparison groups	BI 655130 high dose v Placebo matching to BI 655130
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other ^[5]
Method	Wilson/Newcombe
Parameter estimate	Risk difference (RD)
Point estimate	0.078
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	0.338

Notes:

[5] - No formal hypothesis testing was performed in this trial.

Primary: Number of participants with drug-related Adverse Events (AEs)

End point title	Number of participants with drug-related Adverse Events
End point description:	
Number of participants with drug-related AEs are presented. Safety analysis set (SAF): This set included all randomised patients who received at least one dose of study drug.	
End point type	Primary
End point timeframe:	
From first drug administration until 16 weeks after the last drug administration, up to 32 weeks.	

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested.

End point values	BI 655130 low dose	BI 655130 high dose	Placebo matching to BI 655130	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19 ^[7]	19 ^[8]	21 ^[9]	
Units: Participants	8	8	9	

Notes:

[7] - SAF

[8] - SAF

[9] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: ppPASI 75 at week 16

End point title	ppPASI 75 at week 16
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End point description:

Percentage of participants who achieved >75% reduction in ppPASI score was assessed by ppPASI75. ppPASI is modification of PASI score and an investigator assessment of the extent and severity of pustular and plaque lesions on the palms and soles presenting in PPP participants. This tool provides a numeric scoring for participants overall PPP disease state, ranging from 0 to maximum 72, where 0 corresponds to no signs of psoriasis. It is a linear combination of the percent of surface area of skin that is affected on the palms and soles and the severity of Erythema (E), Pustules (P) (total), and scaling (Desquamation (D)). Missing values for severity or area of involvement were not imputed. ppPASI was calculated as a weighted sum of the scores obtained for E, P, D and Area affected (in%) (where area assessed is glabrous skin on the palms/ soles) (A): $[(E+P+D) \times A \times 0.2 \text{ (right palm)}] + [(E+P+D) \times A \times 0.2 \text{ (left palm)}] + [(E+P+D) \times A \times 0.3 \text{ (right sole)}] + [(E+P+D) \times A \times 0.3 \text{ (left sole)}]$.

End point type	Secondary
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End point timeframe:

Week 16

End point values	BI 655130 low dose	BI 655130 high dose	Placebo matching to BI 655130	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19 ^[10]	19 ^[11]	21 ^[12]	
Units: Percentage of participants (%)				
number (not applicable)	0.0	21.1	9.5	

Notes:

[10] - FAS (NRI)

[11] - FAS (NRI)

[12] - FAS (NRI)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

95% CIs are calculated using the method of Wilson/Newcombe. Unadjusted absolute risk difference versus placebo was calculated as the difference in the observed proportion of patients with ppPASI50 at Week 16 for each treatment scenario, for the FAS.

Comparison groups	BI 655130 low dose v Placebo matching to BI 655130
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other ^[13]
Method	Wilson/Newcombe
Parameter estimate	Risk difference (RD)
Point estimate	-0.095
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.289
upper limit	0.086

Notes:

[13] - No formal hypothesis testing was performed in this trial.

Statistical analysis title	Statistical Analysis 2
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Statistical analysis description:

95% CIs are calculated using the method of Wilson/Newcombe. Unadjusted absolute risk difference versus placebo was calculated as the difference in the observed proportion of patients with ppPASI50 at Week 16 for each treatment scenario, for the FAS.

Comparison groups	BI 655130 high dose v Placebo matching to BI 655130
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other ^[14]
Method	Wilson/Newcombe
Parameter estimate	Risk difference (RD)
Point estimate	0.115
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.116
upper limit	0.348

Notes:

[14] - No formal hypothesis testing was performed in this trial.

Secondary: Percent change from baseline in the ppPASI at week 16

End point title	Percent change from baseline in the ppPASI at week 16
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End point description:

ppPASI is modification of PASI score and an investigator assessment of extent and severity of pustular and plaque lesions on the palms and soles presenting in PPP participants. This tool provides numeric scoring for participants overall PPP disease state, ranging from 0 to maximum 72, where 0 corresponds to no signs of psoriasis. It is a linear combination of the percent of surface area of skin that is affected on the palms and soles and the severity of Erythema(E), Pustules(P)(total), and scaling(Desquamation(D)). Missing values for severity or area of involvement were not imputed. ppPASI was calculated as a weighted sum of the scores obtained for E,P,D and Area affected (in%) (where area assessed is glabrous skin on the palms/ soles) (A): $[(E+P+D) \times A \times 0.2 \text{ (right palm)}] + [(E+P+D) \times A \times 0.2 \text{ (left palm)}] + [(E+P+D) \times A \times 0.3 \text{ (right sole)}] + [(E+P+D) \times A \times 0.3 \text{ (left sole)}]$. Patients from FAS with observed cases (OC) were included for analysis of this endpoint.(FAS (OC))

End point type	Secondary
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End point values	BI 655130 low dose	BI 655130 high dose	Placebo matching to BI 655130	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15 ^[15]	14 ^[16]	15 ^[17]	
Units: Unit on scale				
arithmetic mean (standard deviation)	-32.74 (± 38.52)	-45.80 (± 27.00)	-39.97 (± 32.94)	

Notes:

[15] - FAS (OC)

[16] - FAS (OC)

[17] - FAS (OC)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: CIs were based on Student's t-distribution.	
Comparison groups	BI 655130 low dose v Placebo matching to BI 655130
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other ^[18]
Method	Student's t-distribution
Parameter estimate	Mean difference (final values)
Point estimate	7.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.01
upper limit	34.48

Notes:

[18] - No formal hypothesis testing was performed in this trial.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: CIs were based on Student's t-distribution.	
Comparison groups	BI 655130 high dose v Placebo matching to BI 655130
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	other ^[19]
Method	Student's t-distribution
Parameter estimate	Mean difference (final values)
Point estimate	-5.82

Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.35
upper limit	16.7

Notes:

[19] - No formal hypothesis testing was performed in this trial.

Secondary: Percentage of participants achieving treatment success (treatment success defined as achieving a clinical response of 0 or 1=clear/almost clear) via Palmoplantar Pustulosis Physicians Global Assessment (pppPGA) at week 16

End point title	Percentage of participants achieving treatment success (treatment success defined as achieving a clinical response of 0 or 1=clear/almost clear) via Palmoplantar Pustulosis Physicians Global Assessment (pppPGA) at week 16
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End point description:

pppPGA was relied on the participant's overall skin lesions status on the lesions of the most severely affected palmoplantar surface of the palms and sole was assessed by investigator as clear (0), almost clear (1), mild (2), moderate (3) and severe (4) at week 16. Score Wording were: 0 = Clear = No signs of PPP; no scaling or crusts or pustule remains. 1 = Almost clear = Slight scaling and/or erythema and / or slight crusts; very few new (yellow) and / or old (brown) pustules. 2 = Mild = Scaling and/or erythema and/or crusts; visible new (yellow) and/or old (brown) pustules of limited number and extent. 3 = Moderate = Prominent scaling and/or erythema and / or crusting; prominent new (yellow) and / or old (brown) pustules covering most of the area involved. 4 = Severe = Severe scaling and/or erythema and / or crusting; numerous new (yellow) or old (brown) pustules with and/or without major confluence covering the entire area of at least 2 palmoplantar surfaces.

End point type	Secondary
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End point timeframe:

Week 16

End point values	BI 655130 low dose	BI 655130 high dose	Placebo matching to BI 655130	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19 ^[20]	19 ^[21]	21 ^[22]	
Units: Percentage of participants (%)				
number (not applicable)	0.0	15.8	14.3	

Notes:

[20] - FAS (NRI)

[21] - FAS (NRI)

[22] - FAS (NRI)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

95% CIs are calculated using the method of Wilson/Newcombe.

Comparison groups	BI 655130 low dose v Placebo matching to BI 655130
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Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other ^[23]
Method	Wilson/Newcombe
Parameter estimate	Risk difference (RD)
Point estimate	-0.143
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.346
upper limit	0.049

Notes:

[23] - No formal hypothesis testing was performed in this trial.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
95% CIs are calculated using the method of Wilson/Newcombe.	
Comparison groups	BI 655130 high dose v Placebo matching to BI 655130
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other ^[24]
Method	Wilson/Newcombe
Parameter estimate	Risk difference (RD)
Point estimate	0.015
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.213
upper limit	0.252

Notes:

[24] - No formal hypothesis testing was performed in this trial.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first drug administration until 16 weeks after the last drug administration, up to 32 weeks.

Adverse event reporting additional description:

Analysis set for safety presentation was Safety analysis set (SAF). SAF included all randomised patients who received at least one dose of study drug.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.1
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Reporting groups

Reporting group title	BI 655130 low dose
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Reporting group description:

Participants were administered low dose BI 655130 solution for infusion intravenously every 4 weeks at Day 1, 29, 57 and 85 until 12 weeks.

Reporting group title	BI 655130 high dose
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Reporting group description:

Participants were administered high dose BI 655130 solution for infusion intravenously every 4 weeks at Day 1, 29, 57 and 85 until 12 weeks.

Reporting group title	Placebo matching to BI 655130
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Reporting group description:

Participants were administered placebo matching to BI 655130 solution for infusion intravenously every 4 weeks at Day 1, 29, 57 and 85 until 12 weeks.

Serious adverse events	BI 655130 low dose	BI 655130 high dose	Placebo matching to BI 655130
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	1 / 21 (4.76%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
VIth nerve paralysis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 21 (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
Skin and subcutaneous tissue disorders			
Palmoplantar pustulosis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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	BI 655130 low dose	BI 655130 high dose	Placebo matching to BI 655130
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 19 (89.47%)	17 / 19 (89.47%)	15 / 21 (71.43%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign neoplasm of thyroid gland			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Skin papilloma			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Haematoma			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Hot flush			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	1 / 19 (5.26%)	1 / 19 (5.26%)	0 / 21 (0.00%)
occurrences (all)	1	2	0
General disorders and administration site conditions			
Administration site extravasation			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Catheter site haematoma			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Injection site bruising			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0

Oedema peripheral subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 19 (0.00%) 0	1 / 21 (4.76%) 1
Pyrexia subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 19 (0.00%) 0	0 / 21 (0.00%) 0
Reproductive system and breast disorders			
Breast pain subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1	0 / 21 (0.00%) 0
Dysmenorrhoea subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1	0 / 21 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	3 / 19 (15.79%) 3	2 / 19 (10.53%) 2	1 / 21 (4.76%) 1
Asthma subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1	0 / 21 (0.00%) 0
Catarrh subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 19 (0.00%) 0	0 / 21 (0.00%) 0
Dysphonia subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 19 (0.00%) 0	0 / 21 (0.00%) 0
Epistaxis subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 19 (0.00%) 0	0 / 21 (0.00%) 0
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	1 / 19 (5.26%) 1	1 / 21 (4.76%) 1
Rhinitis allergic subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1	0 / 21 (0.00%) 0
Psychiatric disorders			

Insomnia subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	1 / 19 (5.26%) 1	1 / 21 (4.76%) 1
Investigations			
Lipase increased subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	2 / 19 (10.53%) 3	1 / 21 (4.76%) 1
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 19 (0.00%) 0	1 / 21 (4.76%) 1
Amylase increased subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1	1 / 21 (4.76%) 1
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 19 (0.00%) 0	0 / 21 (0.00%) 0
Blood urine present subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1	0 / 21 (0.00%) 0
C-reactive protein increased subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 19 (0.00%) 0	0 / 21 (0.00%) 0
White blood cells urine positive subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1	0 / 21 (0.00%) 0
Injury, poisoning and procedural complications			
Epicondylitis subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 19 (0.00%) 0	0 / 21 (0.00%) 0
Post-traumatic neck syndrome subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1	0 / 21 (0.00%) 0
Procedural pain subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 2	1 / 19 (5.26%) 1	0 / 21 (0.00%) 0
Thermal burn			

subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1	0 / 21 (0.00%) 0
Cardiac disorders			
Bundle branch block subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 19 (0.00%) 0	0 / 21 (0.00%) 0
Cardiovascular disorder subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1	0 / 21 (0.00%) 0
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	4 / 19 (21.05%) 8	6 / 19 (31.58%) 8	7 / 21 (33.33%) 10
Burning sensation subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 19 (0.00%) 0	0 / 21 (0.00%) 0
Presyncope subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 19 (0.00%) 0	1 / 21 (4.76%) 1
Sciatica subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 19 (0.00%) 0	0 / 21 (0.00%) 0
Somnolence subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 19 (0.00%) 0	0 / 21 (0.00%) 0
Syncope subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1	0 / 21 (0.00%) 0
Tension headache subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1	0 / 21 (0.00%) 0
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 19 (0.00%) 0	0 / 21 (0.00%) 0
Leukocytosis			

subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 2	0 / 19 (0.00%) 0	1 / 21 (4.76%) 1
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 19 (0.00%) 0	0 / 21 (0.00%) 0
Eye disorders Eye inflammation subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1	0 / 21 (0.00%) 0
Lacrimation increased subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1	0 / 21 (0.00%) 0
Ocular hyperaemia subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1	0 / 21 (0.00%) 0
Vitreous floaters subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1	0 / 21 (0.00%) 0
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 19 (0.00%) 0	2 / 21 (9.52%) 2
Abdominal pain upper subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1	1 / 21 (4.76%) 1
Diarrhoea subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	1 / 19 (5.26%) 1	1 / 21 (4.76%) 1
Dry mouth subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1	0 / 21 (0.00%) 0
Flatulence subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 19 (0.00%) 0	0 / 21 (0.00%) 0
Gastric ulcer			

subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Palmoplantar pustulosis			
subjects affected / exposed	2 / 19 (10.53%)	3 / 19 (15.79%)	3 / 21 (14.29%)
occurrences (all)	2	3	3
Acne			
subjects affected / exposed	1 / 19 (5.26%)	2 / 19 (10.53%)	0 / 21 (0.00%)
occurrences (all)	1	2	0
Alopecia			
subjects affected / exposed	0 / 19 (0.00%)	2 / 19 (10.53%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Pruritus			
subjects affected / exposed	0 / 19 (0.00%)	2 / 19 (10.53%)	0 / 21 (0.00%)
occurrences (all)	0	2	0
Psoriasis			
subjects affected / exposed	0 / 19 (0.00%)	2 / 19 (10.53%)	1 / 21 (4.76%)
occurrences (all)	0	2	1
Angioedema			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Dermal cyst			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Dermatitis acneiform			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Dermatitis contact			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Erythema			
subjects affected / exposed	1 / 19 (5.26%)	1 / 19 (5.26%)	0 / 21 (0.00%)
occurrences (all)	1	1	0

Hyperkeratosis subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1	0 / 21 (0.00%) 0
Nail dystrophy subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1	0 / 21 (0.00%) 0
Urticaria subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1	0 / 21 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	3 / 19 (15.79%) 3	2 / 19 (10.53%) 2	1 / 21 (4.76%) 1
Back pain subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	2 / 19 (10.53%) 2	1 / 21 (4.76%) 1
Myalgia subjects affected / exposed occurrences (all)	2 / 19 (10.53%) 2	0 / 19 (0.00%) 0	0 / 21 (0.00%) 0
Muscle spasms subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	0 / 19 (0.00%) 0	2 / 21 (9.52%) 2
Intervertebral disc protrusion subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1	0 / 21 (0.00%) 0
Osteoarthritis subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 19 (0.00%) 0	0 / 21 (0.00%) 0
Pain in extremity subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1	1 / 21 (4.76%) 1
Pain in jaw subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 19 (5.26%) 1	0 / 21 (0.00%) 0
Psoriatic arthropathy			

subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 19 (0.00%) 0	1 / 21 (4.76%) 1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 19 (26.32%)	8 / 19 (42.11%)	8 / 21 (38.10%)
occurrences (all)	10	9	9
Urinary tract infection			
subjects affected / exposed	1 / 19 (5.26%)	3 / 19 (15.79%)	1 / 21 (4.76%)
occurrences (all)	1	3	1
Oral herpes			
subjects affected / exposed	2 / 19 (10.53%)	0 / 19 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Rhinitis			
subjects affected / exposed	1 / 19 (5.26%)	1 / 19 (5.26%)	2 / 21 (9.52%)
occurrences (all)	1	2	2
Bronchitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Cystitis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Gastroenteritis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Periodontitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Alcohol intolerance			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Diabetes mellitus			

subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 21 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 August 2017	With the first protocol amendment, the biopsy procedure was clarified and the pain visual analogue scale (VAS) description was aligned with the instructions given to the patients.
08 May 2018	With the second protocol amendment, the interim analysis once 75% of patients had completed 16 weeks of study was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported