



## Clinical trial results:

## INDUCTION AND MAINTENANCE OF MUCOSAL HEALING IN CROHN'S DISEASE WITH USTEKINUMAB IN CLINICAL PRACTICE

### Summary

EudraCT number	2017-005151-83
Trial protocol	DE
Global end of trial date	30 January 2023

### Results information

Result version number	v1 (current)
This version publication date	17 February 2024
First version publication date	17 February 2024

### Trial information

#### Trial identification

Sponsor protocol code	MUCUS
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#### Additional study identifiers

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

Notes:

### Sponsors

Sponsor organisation name	Charité- Universitätsmedizin Berlin
Sponsor organisation address	Charitéplatz 1, Berlin, Germany, 10117
Public contact	Dr. Andreas Fischer, National Coordinator, Charité Medical School, +49 30450553836, andi.fischer@charite.de
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Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 March 2023
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	30 January 2023
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the real world effectiveness of ustekinumab (routine care) as combined clinical and endoscopic response in week 52.

Protection of trial subjects:

Subjects were instructed to contact the study coordinator/investigator if their health status changed significantly. Ustekinumab was not be administered to a subject with a clinically important, active infection. Investigators evaluated subjects for any signs or symptoms of infection, and also reviewed subjects' diary cards for signs of infection, at scheduled visits. All subjects completed a final follow-up safety assessment 16 weeks after the last administration of ustekinumab in the study.

Background therapy:

Ustekinumab is a fully human immunoglobulin G1 kappa (IgG1k) monoclonal antibody to human IL-12/23p40 that binds with high affinity to the p40 subunit of human IL-12 and IL-23. Inhibition of IL-12 and IL-23 and associated inflammatory pathways via blockade of the shared p40 subunit constitutes a novel mechanism of action for the treatment of Crohn's disease (CD). Since clinical trials rarely represent the real-world patient population and ustekinumab's impact on induction and maintenance of mucosal healing, fistula healing and extraintestinal manifestations are largely unknown and long-term remission, patient reported outcome and quality of life data are incomplete we plan to close these knowledge gaps with a prospective nationwide study in Germany across all care levels.

Evidence for comparator: -

Actual start date of recruitment	31 May 2018
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	Germany: 52
Worldwide total number of subjects	52
EEA total number of subjects	52

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	51
From 65 to 84 years	1
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 10 study centers in Germany, between Date 2018-11-28 and 2023-03-13.

### Pre-assignment

Screening details:

A total of 79 subjects entered the 2-weeks screening period, of whom 52 adult subjects with a Harvey Bradshaw index score of  $\geq 5$  at Baseline and Endoscopy with evidence of active CD (SES-CD score  $\geq 3$ ) were randomized. Subjects will be allowed to intake oral corticosteroids at a prednisone-equivalent dose of  $\leq 40$  mg/day or  $\leq 9$  mg/day of budesonide.

### Period 1

Period 1 title	overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was a prospective, open-label, nationwide, multicenter, national, Phase IV study of ustekinumab in adult subjects with active, moderate to severe, ileal and/or colonic CD. The effectiveness was investigated in a real world setting in 10 German centers representing all care levels - private practice, community hospitals and academic institutions. To ensure a balanced, unbiased real world cohort subjects were stratified 1:1:1 at baseline.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Native

Arm description:

Subjects enrolled are either native to biologic treatment or will have previously had an inadequate response to conventional therapy (no biological treatment)

Arm type	subgroup of real world cohort
Investigational medicinal product name	ustekinumab
Investigational medicinal product code	815610-63-0
Other name	Stelara, SUB27761
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

In week 0, the subjects received a weight-based dose of approximately 6 mg/kg IV induction treatment with ustekinumab. Ustekinumab was administered to each subject over a period of no less than 1 hour. The infusion was to be completed within 5 hours of preparation.

At week 8, all subjects received a 90 mg SC injection of ustekinumab.

The timing of the injections was in line with the GERMAN LABEL for the treatment of CD, where administration at 12-week intervals is recommended. After week 8, the subjects were trained in the self-injection of SC ustekinumab under the guidance of the investigator.

<b>Arm title</b>	Biological-exposed to 1
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Arm description:

subjects with medical contraindications to one previous biologic therapies approved for the treatment of CD in

Germany (i.e., infliximab, adalimumab or vedolizumab).

Arm type	subgroup of real world cohort
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Investigational medicinal product name	ustekinumab
Investigational medicinal product code	815610-63-0
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<b>Arm title</b>	Biological exposed to multiple
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**Arm description:**

subjects with medical contraindications to more than one previous biologic therapies approved for the treatment of CD in Germany (i.e., infliximab, adalimumab or vedolizumab)

Arm type	sub group of real world Cohort
Investigational medicinal product name	ustekinumab
Investigational medicinal product code	815610-63-0
Other name	Stelara, SUB27761
Pharmaceutical forms	Solution for injection
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**Dosage and administration details:**

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<b>Number of subjects in period 1</b>	Native	Biological-exposed to 1	Biological exposed to multiple
Started	13	22	17
Completed	10	14	10
Not completed	3	8	7
Consent withdrawn by subject	1	2	1
unknown	-	1	1
Adverse event, non-fatal	1	1	1
Pregnancy	-	1	-
Non-HBI-Responder	1	3	1
Lost to follow-up	-	-	3

## Baseline characteristics

### Reporting groups

Reporting group title	Native
Reporting group description: Subjects enrolled are either native to biologic treatment or will have previously had an inadequate response to conventional therapy (no biological treatment)	
Reporting group title	Biological-exposed to 1
Reporting group description: subjects with medical contraindications to one previous biologic therapies approved for the treatment of CD in Germany (i.e., infliximab, adalimumab or vedolizumab).	
Reporting group title	Biological exposed to multiple
Reporting group description: subjects with medical contraindications to more than one previous biologic therapies approved for the treatment of CD in Germany (i.e., infliximab, adalimumab or vedolizumab)	

Reporting group values	Native	Biological-exposed to 1	Biological exposed to multiple
Number of subjects	13	22	17
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
median	39.2	36.7	42.4
full range (min-max)	20 to 64	21 to 74	21 to 57
Gender categorical Units: Subjects			
Female	8	14	6
Male	5	8	11
Prior Crohn's Surgery (PCS)			
Prior Crohn 's Surgery			
Units: Subjects			
Yes (PCS)	0	3	4
No (PCS)	13	19	13
Concomitant Monotherapy Immunomodulators (CMI) Units: Subjects			
Yes (CMI)	0	2	1
No (CMI)	13	20	16

Concomitant Combination Therapy Immunomodulators (CCTI) Units: Subjects			
Yes (CCTI)	0	0	0
No (CCTI)	13	22	17
Fistulizing Crohn 's (FC) Units: Subjects			
Yes (FC)	0	2	5
No (FC)	13	20	12
Weight Units: kg median full range (min-max)	75.9 39 to 93	68 51 to 103	72 47 to 106
Height Units: cm median full range (min-max)	169 147 to 195	169 157 to 192	172 161 to 195

<b>Reporting group values</b>	Total		
Number of subjects	52		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years median full range (min-max)	-		
Gender categorical Units: Subjects			
Female	28		
Male	24		
Prior Crohn's Surgery (PCS)			
Prior Crohn 's Surgery Units: Subjects			
Yes (PCS)	7		
No (PCS)	45		
Concomitant Monotherapy Immunomodulators (CMI) Units: Subjects			
Yes (CMI)	3		
No (CMI)	49		
Concomitant Combination Therapy Immunomodulators (CCTI)			

Units: Subjects			
Yes (CCTI)	0		
No (CCTI)	52		
Fistulizing Crohn 's (FC)			
Units: Subjects			
Yes (FC)	7		
No (FC)	45		
Weight			
Units: kg			
median			
full range (min-max)	-		
Height			
Units: cm			
median			
full range (min-max)	-		



## End points

### End points reporting groups

Reporting group title	Native
Reporting group description: Subjects enrolled are either native to biologic treatment or will have previously had an inadequate response to conventional therapy (no biological treatment)	
Reporting group title	Biological-exposed to 1
Reporting group description: subjects with medical contraindications to one previous biologic therapies approved for the treatment of CD in Germany (i.e., infliximab, adalimumab or vedolizumab).	
Reporting group title	Biological exposed to multiple
Reporting group description: subjects with medical contraindications to more than one previous biologic therapies approved for the treatment of CD in Germany (i.e., infliximab, adalimumab or vedolizumab)	

### Primary: ITT-Analysis Clinical and Endoscopic Response at week 52

End point title	ITT-Analysis Clinical and Endoscopic Response at week 52
End point description: Intent-to-Treat Analysis set, N= number of randomized subjects Outcome: Reduction from baseline in SES-CD Score $\geq 50\%$ and Harvey Bradshaw Index decrease $\geq 3$ points	
End point type	Primary
End point timeframe: overall study	

End point values	Native	Biological-exposed to 1	Biological exposed to multiple	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	22	17	
Units: number				
Responder	3	5	5	
Non- Responder	10	17	12	

<b>Attachments (see zip file)</b>	secondary endpoint_clinical remission.pdf
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### Statistical analyses

<b>Statistical analysis title</b>	efficacy Native vs. Biological-exposed to 1
Comparison groups	Biological-exposed to 1 v Native

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.981
Method	Proc Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	5.209

<b>Statistical analysis title</b>	efficacy Native vs. Biological exposed multiple
Comparison groups	Native v Biological exposed to multiple
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.698
Method	Proc Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.137
upper limit	3.784

<b>Statistical analysis title</b>	efficacy Biological-exposed to 1 vs. multiple
Comparison groups	Biological-exposed to 1 v Biological exposed to multiple
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.636
Method	Proc Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.706
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.167
upper limit	2.989

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## Primary: PP-Analysis Clinical and Endoscopic Response at week 52

End point title	PP-Analysis Clinical and Endoscopic Response at week 52
End point description:	
Per Protocol Analysis set, N= number of randomized subjects	
Outcome: Reduction from baseline in SES-CD Score $\geq$ 50% and Harvey Bradshaw Index decrease $\geq$ 3 points	
End point type	Primary
End point timeframe:	
52 weeks	

End point values	Native	Biological-exposed to 1	Biological exposed to multiple	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	11	8	
Units: number				
Responder	3	5	5	
Non-Responder	3	6	3	

### Statistical analyses

<b>Statistical analysis title</b>	efficacy Native vs. Biological-exposed to 1
Comparison groups	Native v Biological-exposed to 1
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.858
Method	Proc Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.164
upper limit	8.799

<b>Statistical analysis title</b>	efficacy Native vs. Biological exposed to multiple
Comparison groups	Native v Biological exposed to multiple
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.641
Method	Proc Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	5.136

<b>Statistical analysis title</b>	efficacy Biological-exposed to 1 vs. multiple
Comparison groups	Biological-exposed to 1 v Biological exposed to multiple
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.465
Method	Proc Regression
Parameter estimate	Odds ratio (OR)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.078
upper limit	3.21

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

overall trial

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19
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### Reporting groups

Reporting group title	Native
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Reporting group description: -

Reporting group title	Biological-exposed to 1
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Reporting group description: -

Reporting group title	Biological exposed to multiple
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Reporting group description: -

Serious adverse events	Native	Biological-exposed to 1	Biological exposed to multiple
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 13 (23.08%)	6 / 22 (27.27%)	2 / 17 (11.76%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 22 (4.55%)	0 / 17 (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
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 22 (4.55%)	0 / 17 (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
Pregnancy, puerperium and perinatal conditions			
Abortion missed			
subjects affected / exposed	0 / 13 (0.00%)	1 / 22 (4.55%)	0 / 17 (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
Pregnancy			

subjects affected / exposed	0 / 13 (0.00%)	1 / 22 (4.55%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 22 (4.55%)	0 / 17 (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
General disorders and administration site conditions			
Drug ineffective			
subjects affected / exposed	1 / 13 (7.69%)	0 / 22 (0.00%)	0 / 17 (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
Pyrexia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 22 (4.55%)	1 / 17 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Crohn's disease			
subjects affected / exposed	0 / 13 (0.00%)	3 / 22 (13.64%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileal stenosis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 22 (0.00%)	0 / 17 (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
Subileus			
subjects affected / exposed	1 / 13 (7.69%)	0 / 22 (0.00%)	0 / 17 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis			

subjects affected / exposed	1 / 13 (7.69%)	0 / 22 (0.00%)	0 / 17 (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
<b>Infections and infestations</b>			
Abscess			
subjects affected / exposed	0 / 13 (0.00%)	1 / 22 (4.55%)	0 / 17 (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
<b>COVID-19</b>			
subjects affected / exposed	0 / 13 (0.00%)	1 / 22 (4.55%)	0 / 17 (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
<b>Norovirus infection</b>			
subjects affected / exposed	1 / 13 (7.69%)	0 / 22 (0.00%)	0 / 17 (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: 1 %

<b>Non-serious adverse events</b>	Native	Biological-exposed to 1	Biological exposed to multiple
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 13 (46.15%)	5 / 22 (22.73%)	9 / 17 (52.94%)
<b>Vascular disorders</b>			
Hypertension			
subjects affected / exposed	0 / 13 (0.00%)	1 / 22 (4.55%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
<b>Blood and lymphatic system disorders</b>			
Iron deficiency anaemia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 22 (0.00%)	1 / 17 (5.88%)
occurrences (all)	0	0	1
<b>General disorders and administration site conditions</b>			
Injection site erythema			
subjects affected / exposed	0 / 13 (0.00%)	1 / 22 (4.55%)	0 / 17 (0.00%)
occurrences (all)	0	1	0
<b>Gastrointestinal disorders</b>			

Abdominal pain subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 22 (0.00%) 0	0 / 17 (0.00%) 0
Anal fissure subjects affected / exposed occurrences (all)	2 / 13 (15.38%) 2	0 / 22 (0.00%) 0	0 / 17 (0.00%) 0
Anal fistula subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 22 (0.00%) 0	1 / 17 (5.88%) 1
Bile acid malabsorption subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 22 (4.55%) 1	1 / 17 (5.88%) 1
Reproductive system and breast disorders Pruritus genital subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 22 (4.55%) 1	0 / 17 (0.00%) 0
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 22 (0.00%) 0	0 / 17 (0.00%) 0
Cold urticaria subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 22 (4.55%) 1	0 / 17 (0.00%) 0
Eczema subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 22 (0.00%) 0	0 / 17 (0.00%) 0
Photosensitivity reaction subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 22 (0.00%) 0	0 / 17 (0.00%) 0
Pruritus subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 22 (0.00%) 0	1 / 17 (5.88%) 1
Rash subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 22 (0.00%) 0	1 / 17 (5.88%) 1
Endocrine disorders			



Adrenal insufficiency subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 22 (0.00%) 0	1 / 17 (5.88%) 1
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 22 (4.55%) 1	0 / 17 (0.00%) 0
Infections and infestations Gastrointestinal infection subjects affected / exposed occurrences (all)  Nasopharyngitis subjects affected / exposed occurrences (all)  Oral herpes subjects affected / exposed occurrences (all)  Respiratory tract infection subjects affected / exposed occurrences (all)  Urinary tract infection subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0  0 / 13 (0.00%) 0  1 / 13 (7.69%) 1  1 / 13 (7.69%) 1  0 / 13 (0.00%) 0	0 / 22 (0.00%) 0  0 / 22 (0.00%) 0  0 / 22 (0.00%) 0  0 / 22 (0.00%) 0  0 / 22 (0.00%) 0	1 / 17 (5.88%) 1  1 / 17 (5.88%) 1  0 / 17 (0.00%) 0  0 / 17 (0.00%) 0  1 / 17 (5.88%) 1

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 July 2018	Late registration of additional study centers (ICCC Rhein Main/ Isarklinik München/Hamburger Forschungsinstitut CED)
21 December 2020	late registration of study center Universitätsklinik Frankfurt.a. Main
10 September 2021	update protocol Version (09/01/2021)_CNTO 1275 (Ustekinumab/Stelara)

Notes:

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### 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.

The sample size was too small owed to the overall financial budget available and suffered further due to global-pandemic-related factors (sick patients, sick study personnel, limited pharmacy, laboratory in - and out patient services, lost to FU).

Notes: