



Clinical trial results:

Randomised, double-blind, double-dummy, active-controlled, phase III clinical trial on the efficacy and safety of an 8-week add-on treatment with budesonide 9 mg capsules vs. budesonide 6 mg capsules vs. budesonide-MMX® 9 mg tablets in patients with ulcerative colitis refractory to standard treatment with mesalazine.

Summary

EudraCT number	2017-004576-57
Trial protocol	DE LV HU SK LT CZ PL
Global end of trial date	03 October 2022

Results information

Result version number	v1 (current)
This version publication date	05 June 2024
First version publication date	05 June 2024

Trial information

Trial identification

Sponsor protocol code	BUX-4/UCA
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Dr. Falk Pharma GmbH
Sponsor organisation address	Leinenweberstr. 5, Freiburg, Germany, 79108
Public contact	Clinical Research and Development, Dr. Falk Pharma GmbH, +49 76115140, zentrale@drfalkpharma.de
Scientific contact	Clinical Research and Development, Dr. Falk Pharma GmbH, +49 76115140, zentrale@drfalkpharma.de

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	15 December 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 September 2022
Global end of trial reached?	Yes
Global end of trial date	03 October 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to prove the non-inferiority of an 8-week add-on treatment with once-daily 9 mg budesonide capsules and 6 mg budesonide capsules, respectively, versus active comparator 9 mg budesonide-MMX® tablets, for the induction of remission in patients with ulcerative colitis (UC) refractory to standard treatment with mesalazine.

Protection of trial subjects:

Close supervision of subjects by implementing interim visits every 14 days to guarantee their safety and well-being. Prior to recruitment of patients, all relevant documents of the clinical study were submitted and proved by the Independent Ethics Committees (IECs) responsible for the participating investigators. Written consent documents embodied the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for Good Clinical Practice (GCP) and were in accordance with all applicable laws and regulations. The informed consent form and patient information sheet described the planned and permitted uses, transfers and disclosures of the patient's personal data and personal health information for purposes of conducting the study. The informed consent form and the patient information sheet further explained the nature of the study, its objectives and potential risks and benefits as well as the date informed consent was given. Before being enrolled in the clinical trial, every patient was informed that participation in this trial was voluntary and that he/she could withdraw from the study at any time without giving a reason and without having to fear any loss in his/her medical care. The patient's consent was obtained in writing before the start of the study. By signing the informed consent, the patient declared that he/she was participating voluntarily and intended to follow the study protocol instructions and the instructions of the investigator and to answer the questions asked during the course of the trial.

Background therapy:

Patients enrolled in this trial had to be on treatment with approved oral mesalazine formulations for at least 6 weeks prior to baseline at a mesalazine dosage of ≥ 2.4 g/d, or therapeutic aminosalicylate equivalent, i.e. either olsalazine ≥ 2.4 g/d, or balsalazide ≥ 5.6 g/d, or sulfasalazine ≥ 6.2 g/d. The dose, formulation and intake regimen of oral mesalazine used prior to baseline had to be kept stable for 6 weeks until baseline.

Alternatively, patients had to be on treatment with a combinatory treatment with approved oral mesalazine formulations at a dosage of ≥ 2.4 g/d (or therapeutic equivalent) and an approved rectal mesalazine formulation (in a registered dose for treatment of an acute episode of distal UC) for at least 10 days prior to baseline. The dose, formulation and intake regimen of combined (oral and rectal) mesalazine (if applicable) had to be kept stable for at least 10 days until baseline.

The oral mesalazine treatment had to be continued. The dose, formulation and intake regimen of oral mesalazine treatment had to be kept stable from baseline throughout the trial until end of tapering phase. Rectal mesalazine treatment had to be stopped at baseline.

Evidence for comparator:

Cortiment® MMX® (budesonide-MMX®) is the only approved budesonide formulation for the induction of remission in patients with active, mild to moderate UC refractory to mesalazine standard treatment.

Actual start date of recruitment	01 March 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 41
Country: Number of subjects enrolled	Slovakia: 11
Country: Number of subjects enrolled	Czechia: 9
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Latvia: 27
Country: Number of subjects enrolled	Lithuania: 14
Country: Number of subjects enrolled	Russian Federation: 170
Country: Number of subjects enrolled	Türkiye: 14
Country: Number of subjects enrolled	Ukraine: 188
Worldwide total number of subjects	482
EEA total number of subjects	110

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)	448
From 65 to 84 years	34
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In total, 482 patients were randomized and treated in the Czech Republic, Germany, Hungary, Latvia, Lithuania, Poland, the Russian Federation, Slovakia, Turkey and Ukraine.

Pre-assignment

Screening details:

Patients signing the informed consent form were screened for up to 2 weeks to evaluate eligibility for the study. A total of 648 patients was screened for enrollment into the study. One hundred and sixty-six patients were neither randomized nor treated. The most common reason for screening failure was violation of eligibility criteria.

Period 1

Period 1 title	8-week double-blind treatment phase (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

The study was conducted using the double-dummy technique to guarantee the double-blinding.

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A (BUX-9 mg)

Arm description:

8-week treatment with 1 budesonide 9 mg capsule and 1 placebo budesonide-MMX® tablet

Arm type	Experimental
Investigational medicinal product name	Budenofalk® 9 mg capsule
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1 capsule Budenofalk® 9 mg granules once daily in the morning

Investigational medicinal product name	Budesonide-MMX® placebo tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 placebo budesonide-MMX® tablet per day in the morning

Arm title	Group B (BUX-6 mg)
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Arm description:

8-week treatment with 1 budesonide 6 mg capsule and 1 placebo budesonide-MMX® tablet

Arm type	Experimental
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Investigational medicinal product name	Budenofalk® 6 mg capsule
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1 capsule Budenofalk® 6 mg granules once daily in the morning

Investigational medicinal product name	Budesonide-MMX® placebo tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 placebo budesonide-MMX® tablet per day in the morning

Arm title	Group C (MMX-9 mg)
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Arm description:

8-week treatment with 1 placebo budesonide capsule and 1 budesonide-MMX® 9 mg tablet

Arm type	Active comparator
Investigational medicinal product name	Budesonide placebo capsule
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1 placebo budesonide capsule once daily in the morning

Investigational medicinal product name	Budesonide-MMX® 9 mg tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 budesonide-MMX® 9 mg tablet once daily in the morning

Number of subjects in period 1	Group A (BUX-9 mg)	Group B (BUX-6 mg)	Group C (MMX-9 mg)
Started	159	164	159
Completed	149	158	149
Not completed	10	6	10
Adverse event, non-fatal	2	2	2
Other reasons	3	-	2
Lack of patient's cooperation	1	1	2
Lack of efficacy	4	3	4

Baseline characteristics

Reporting groups

Reporting group title	Group A (BUX-9 mg)
Reporting group description:	
8-week treatment with 1 budesonide 9 mg capsule and 1 placebo budesonide-MMX® tablet	
Reporting group title	Group B (BUX-6 mg)
Reporting group description:	
8-week treatment with 1 budesonide 6 mg capsule and 1 placebo budesonide-MMX® tablet	
Reporting group title	Group C (MMX-9 mg)
Reporting group description:	
8-week treatment with 1 placebo budesonide capsule and 1 budesonide-MMX® 9 mg tablet	

Reporting group values	Group A (BUX-9 mg)	Group B (BUX-6 mg)	Group C (MMX-9 mg)
Number of subjects	159	164	159
Age categorical			
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)	148	148	152
From 65-84 years	11	16	7
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	42.1	42.3	40.9
standard deviation	± 12.86	± 13.87	± 12.58
Gender categorical			
Units: Subjects			
Female	69	78	73
Male	90	86	86

Reporting group values	Total		
Number of subjects	482		
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)	448		
From 65-84 years	34		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	220		
Male	262		

End points

End points reporting groups

Reporting group title	Group A (BUX-9 mg)
Reporting group description: 8-week treatment with 1 budesonide 9 mg capsule and 1 placebo budesonide-MMX® tablet	
Reporting group title	Group B (BUX-6 mg)
Reporting group description: 8-week treatment with 1 budesonide 6 mg capsule and 1 placebo budesonide-MMX® tablet	
Reporting group title	Group C (MMX-9 mg)
Reporting group description: 8-week treatment with 1 placebo budesonide capsule and 1 budesonide-MMX® 9 mg tablet	

Primary: Clinical and endoscopic remission at week 8 / EOT (PP final)

End point title	Clinical and endoscopic remission at week 8 / EOT (PP final)
End point description: Percentage of patients being in clinical and endoscopic remission at week 8 / EOT. The primary efficacy variable was defined as an abbreviated mDAI total score ≤ 2 with <ul style="list-style-type: none">• mDAI subscore for rectal bleeding = 0,• mDAI subscore for stool frequency ≤ 1, and• mDAI subscore for mucosal appearance ≤ 1. The analysis set is the per-protocol analysis set for the final analysis (N = 431).	
End point type	Primary
End point timeframe: After 8-week treatment: week 8 / EOT	

End point values	Group A (BUX-9 mg)	Group B (BUX-6 mg)	Group C (MMX-9 mg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	144	145	142	
Units: Subjects				
Yes	76	76	78	
No	68	69	64	

Statistical analyses

Statistical analysis title	Non-inferiority test (BUX-9 mg vs. MMX-9 mg)
Statistical analysis description: For statistical testing a non-inferiority margin of 10% was defined. Hence, non-inferiority is shown if the lower bound of the 95% repeated confidence interval for the treatment difference with respect to clinical and endoscopic remission (nBUX-9 mg – nMMX-9 mg) is above -10%. This corresponds to a local significance level of 0.0232 for the final analysis.	
Comparison groups	Group A (BUX-9 mg) v Group C (MMX-9 mg)

Number of subjects included in analysis	286
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0905 ^[1]
Method	Farrington-Manning test
Parameter estimate	Risk difference (RD)
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.7
upper limit	9.4

Notes:

[1] - As the p-value is above the local significance level of 0.0232, non-inferiority has not been proven for the PP analysis set for the final analysis.

Statistical analysis title	Non-inferiority test (BUX-6 mg vs. MMX-9 mg)
Comparison groups	Group B (BUX-6 mg) v Group C (MMX-9 mg)
Number of subjects included in analysis	287
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[2]
P-value	= 0.1007
Method	Farrington-Manning test
Parameter estimate	Risk difference (RD)
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14
upper limit	9.1

Notes:

[2] - For statistical testing a non-inferiority margin of 10% was defined. Hence, non-inferiority is shown if the lower bound of the 95% repeated confidence interval for the treatment difference with respect to clinical and endoscopic remission (nBUX-6 mg – nMMX-9 mg) is above -10%. This corresponds to a local significance level of 0.0232 for the final analysis.

Primary: Clinical and endoscopic remission at week 8 / EOT (FAS final)

End point title	Clinical and endoscopic remission at week 8 / EOT (FAS final)
End point description:	
Percentage of patients being in clinical and endoscopic remission at week 8 / EOT. The primary efficacy variable was defined as an abbreviated mDAI total score ≤ 2 with	
<ul style="list-style-type: none"> • mDAI subscore for rectal bleeding = 0, • mDAI subscore for stool frequency ≤ 1, and • mDAI subscore for mucosal appearance ≤ 1. 	
The analysis set is the full analysis set for the final analysis (N = 482).	
End point type	Primary
End point timeframe:	
After 8-week treatment: week 8 / EOT	

End point values	Group A (BUX-9 mg)	Group B (BUX-6 mg)	Group C (MMX-9 mg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	159	164	159	
Units: Subjects				
Yes	82	82	86	
No / missing	77	82	73	

Statistical analyses

Statistical analysis title	Non-inferiority test (BUX-9 mg vs. MMX-9 mg)
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Statistical analysis description:

For statistical testing a non-inferiority margin of 10% was defined. Hence, non-inferiority is shown if the lower bound of the 95% repeated confidence interval for the treatment difference with respect to clinical and endoscopic remission ($n_{BUX-9\text{ mg}} - n_{MMX-9\text{ mg}}$) is above -10%. This corresponds to a local significance level of 0.0232 for the final analysis.

Comparison groups	Group A (BUX-9 mg) v Group C (MMX-9 mg)
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0896 ^[3]
Method	Farrington-Manning test
Parameter estimate	Risk difference (RD)
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.5
upper limit	8.5

Notes:

[3] - As the p-value is above the local significance level of 0.0232, non-inferiority has not been proven for the FAS analysis set for final analysis.

Statistical analysis title	Non-inferiority test (BUX-6 mg vs. MMX-9 mg)
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Statistical analysis description:

For statistical testing a non-inferiority margin of 10% was defined. Hence, non-inferiority is shown if the lower bound of the 95% repeated confidence interval for the treatment difference with respect to clinical and endoscopic remission ($n_{BUX-6\text{ mg}} - n_{MMX-9\text{ mg}}$) is above -10%. This corresponds to a local significance level of 0.0232 for the final analysis.

Comparison groups	Group B (BUX-6 mg) v Group C (MMX-9 mg)
Number of subjects included in analysis	323
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.1426 ^[4]
Method	Farrington-Manning test
Parameter estimate	Risk difference (RD)
Point estimate	-4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15
upper limit	6.8

Notes:

[4] - As the p-value is above the local significance level of 0.0232, non-inferiority has not been proven for the FAS analysis set for final analysis.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Period 1: 8-week double-blind treatment phase

Period 2: 2-week double-blind tapering phase

Period 3: 2-week follow-up phase

Adverse event reporting additional description:

Period 1: Group A, Group B, Group C (safety analysis set)

Period 2: Group A1, Group A2, Group B1, Group B2, Group C1, Group C2 (safety analysis set)

Period 3: Former Group A, Former Group B, Former Group C (safety analysis set)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.0
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Reporting groups

Reporting group title	Group A (BUX-9 mg)
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Reporting group description:

8-week treatment with 1 budesonide 9 mg capsule and 1 placebo budesonide-MMX® tablet

Reporting group title	Group B (BUX-6 mg)
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Reporting group description:

8-week treatment with 1 budesonide 6 mg capsule and 1 placebo budesonide-MMX® tablet

Reporting group title	Group C (MMX-9 mg)
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Reporting group description:

8-week treatment with 1 placebo budesonide capsule and 1 budesonide-MMX® 9 mg tablet

Reporting group title	Group A1 (BUX-9 mg-V)
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Reporting group description:

2-week double-blind treatment with 1 budesonide 9 mg capsule every other day and 1 placebo budesonide-MMX® tablet every other day

Reporting group title	Group A2 (BUX-9 mg-P)
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Reporting group description:

2-week double-blind treatment with 1 placebo budesonide capsule every other day and 1 placebo budesonide-MMX® tablet every other day

Reporting group title	Group B1 (BUX-6 mg-V)
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Reporting group description:

2-week double-blind treatment with 1 budesonide 6 mg capsule every other day and 1 placebo budesonide-MMX® tablet every other day

Reporting group title	Group B2 (BUX-6 mg-P)
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Reporting group description:

2-week double-blind treatment with 1 placebo budesonide capsule every other day and 1 placebo budesonide-MMX® tablet every other day

Reporting group title	Group C1 (MMX-9 mg-V)
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Reporting group description:

2-week double-blind treatment with 1 placebo budesonide capsule every other day and 1 budesonide-MMX® tablet every other day

Reporting group title	Group C2 (MMX-9 mg-P)
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Reporting group description:

2-week double-blind treatment with 1 placebo budesonide capsule every other day and 1 placebo budesonide-MMX® tablet every other day

Reporting group title	Former Group A (BUX-9 mg)
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Reporting group description:

8-week treatment with 1 budesonide 9 mg capsule and 1 placebo budesonide-MMX® tablet

Reporting group title	Former Group B (BUX-6 mg)
Reporting group description:	
8-week treatment with 1 budesonide 6 mg capsule and 1 placebo budesonide-MMX® tablet	
Reporting group title	Former Group C (MMX-9 mg)
Reporting group description:	
8-week treatment with 1 placebo budesonide capsule and 1 budesonide-MMX® 9 mg tablet	

Serious adverse events	Group A (BUX-9 mg)	Group B (BUX-6 mg)	Group C (MMX-9 mg)
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 159 (2.52%)	4 / 164 (2.44%)	0 / 159 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 159 (0.63%)	1 / 164 (0.61%)	0 / 159 (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			
Fatigue			
subjects affected / exposed	0 / 159 (0.00%)	1 / 164 (0.61%)	0 / 159 (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
Gastrointestinal disorders			
Colitis ulcerative			
subjects affected / exposed	1 / 159 (0.63%)	1 / 164 (0.61%)	0 / 159 (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
Vomiting			
subjects affected / exposed	0 / 159 (0.00%)	1 / 164 (0.61%)	0 / 159 (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
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 159 (0.63%)	0 / 164 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory tract infection viral subjects affected / exposed	1 / 159 (0.63%)	0 / 164 (0.00%)	0 / 159 (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
Atypical pneumonia subjects affected / exposed	0 / 159 (0.00%)	0 / 164 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Group A1 (BUX-9 mg-V)	Group A2 (BUX-9 mg-P)	Group B1 (BUX-6 mg-V)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 77 (0.00%)	1 / 82 (1.22%)	0 / 86 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 77 (0.00%)	0 / 82 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 77 (0.00%)	0 / 82 (0.00%)	0 / 86 (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			
Colitis ulcerative			
subjects affected / exposed	0 / 77 (0.00%)	1 / 82 (1.22%)	0 / 86 (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
Vomiting			
subjects affected / exposed	0 / 77 (0.00%)	0 / 82 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			

subjects affected / exposed	0 / 77 (0.00%)	0 / 82 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection viral			
subjects affected / exposed	0 / 77 (0.00%)	0 / 82 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical pneumonia			
subjects affected / exposed	0 / 77 (0.00%)	0 / 82 (0.00%)	0 / 86 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Group B2 (BUX-6 mg-P)	Group C1 (MMX-9 mg-V)	Group C2 (MMX-9 mg-P)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 78 (0.00%)	0 / 81 (0.00%)	0 / 78 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 78 (0.00%)	0 / 81 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 78 (0.00%)	0 / 81 (0.00%)	0 / 78 (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			
Colitis ulcerative			
subjects affected / exposed	0 / 78 (0.00%)	0 / 81 (0.00%)	0 / 78 (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
Vomiting			

subjects affected / exposed	0 / 78 (0.00%)	0 / 81 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 78 (0.00%)	0 / 81 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection viral			
subjects affected / exposed	0 / 78 (0.00%)	0 / 81 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical pneumonia			
subjects affected / exposed	0 / 78 (0.00%)	0 / 81 (0.00%)	0 / 78 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Former Group A (BUX-9 mg)	Former Group B (BUX-6 mg)	Former Group C (MMX-9 mg)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 159 (0.00%)	0 / 164 (0.00%)	2 / 159 (1.26%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 159 (0.00%)	0 / 164 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 159 (0.00%)	0 / 164 (0.00%)	0 / 159 (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			
Colitis ulcerative			

subjects affected / exposed	0 / 159 (0.00%)	0 / 164 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 159 (0.00%)	0 / 164 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 159 (0.00%)	0 / 164 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection viral			
subjects affected / exposed	0 / 159 (0.00%)	0 / 164 (0.00%)	0 / 159 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical pneumonia			
subjects affected / exposed	0 / 159 (0.00%)	0 / 164 (0.00%)	1 / 159 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Group A (BUX-9 mg)	Group B (BUX-6 mg)	Group C (MMX-9 mg)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 159 (15.72%)	31 / 164 (18.90%)	32 / 159 (20.13%)
Investigations			
Cortisol decreased			
subjects affected / exposed	8 / 159 (5.03%)	6 / 164 (3.66%)	24 / 159 (15.09%)
occurrences (all)	9	7	27
Alanine aminotransferase increased			
subjects affected / exposed	4 / 159 (2.52%)	4 / 164 (2.44%)	3 / 159 (1.89%)
occurrences (all)	4	4	3
Lipase increased			

subjects affected / exposed occurrences (all)	5 / 159 (3.14%) 5	3 / 164 (1.83%) 3	3 / 159 (1.89%) 3
White blood cell count increased subjects affected / exposed occurrences (all)	3 / 159 (1.89%) 3	4 / 164 (2.44%) 5	2 / 159 (1.26%) 3
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	2 / 159 (1.26%) 2	4 / 164 (2.44%) 4	1 / 159 (0.63%) 1
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	1 / 159 (0.63%) 1	4 / 164 (2.44%) 6	0 / 159 (0.00%) 0
Nervous system disorders Headache subjects affected / exposed occurrences (all)	11 / 159 (6.92%) 17	10 / 164 (6.10%) 10	7 / 159 (4.40%) 12
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 159 (0.63%) 1	4 / 164 (2.44%) 4	1 / 159 (0.63%) 1

Non-serious adverse events	Group A1 (BUX-9 mg-V)	Group A2 (BUX-9 mg-P)	Group B1 (BUX-6 mg-V)
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 77 (0.00%)	2 / 82 (2.44%)	1 / 86 (1.16%)
Investigations Cortisol decreased subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	0 / 82 (0.00%) 0	0 / 86 (0.00%) 0
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	0 / 82 (0.00%) 0	0 / 86 (0.00%) 0
Lipase increased subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	0 / 82 (0.00%) 0	0 / 86 (0.00%) 0
White blood cell count increased subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	0 / 82 (0.00%) 0	0 / 86 (0.00%) 0

Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	0 / 82 (0.00%) 0	0 / 86 (0.00%) 0
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	0 / 82 (0.00%) 0	0 / 86 (0.00%) 0
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	2 / 82 (2.44%) 2	1 / 86 (1.16%) 1
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	0 / 77 (0.00%) 0	0 / 82 (0.00%) 0	0 / 86 (0.00%) 0

Non-serious adverse events	Group B2 (BUX-6 mg-P)	Group C1 (MMX-9 mg-V)	Group C2 (MMX-9 mg-P)
Total subjects affected by non-serious adverse events subjects affected / exposed	2 / 78 (2.56%)	1 / 81 (1.23%)	0 / 78 (0.00%)
Investigations Cortisol decreased subjects affected / exposed occurrences (all)	0 / 78 (0.00%) 0	0 / 81 (0.00%) 0	0 / 78 (0.00%) 0
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 78 (0.00%) 0	0 / 81 (0.00%) 0	0 / 78 (0.00%) 0
Lipase increased subjects affected / exposed occurrences (all)	0 / 78 (0.00%) 0	0 / 81 (0.00%) 0	0 / 78 (0.00%) 0
White blood cell count increased subjects affected / exposed occurrences (all)	0 / 78 (0.00%) 0	0 / 81 (0.00%) 0	0 / 78 (0.00%) 0
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	0 / 78 (0.00%) 0	0 / 81 (0.00%) 0	0 / 78 (0.00%) 0
Aspartate aminotransferase increased			

subjects affected / exposed occurrences (all)	0 / 78 (0.00%) 0	0 / 81 (0.00%) 0	0 / 78 (0.00%) 0
Nervous system disorders Headache subjects affected / exposed occurrences (all)	2 / 78 (2.56%) 2	1 / 81 (1.23%) 3	0 / 78 (0.00%) 0
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	0 / 78 (0.00%) 0	0 / 81 (0.00%) 0	0 / 78 (0.00%) 0

Non-serious adverse events	Former Group A (BUX-9 mg)	Former Group B (BUX-6 mg)	Former Group C (MMX-9 mg)
Total subjects affected by non-serious adverse events subjects affected / exposed	6 / 159 (3.77%)	3 / 164 (1.83%)	13 / 159 (8.18%)
Investigations Cortisol decreased subjects affected / exposed occurrences (all)	0 / 159 (0.00%) 0	1 / 164 (0.61%) 1	3 / 159 (1.89%) 3
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 159 (0.00%) 0	0 / 164 (0.00%) 0	2 / 159 (1.26%) 2
Lipase increased subjects affected / exposed occurrences (all)	0 / 159 (0.00%) 0	1 / 164 (0.61%) 1	3 / 159 (1.89%) 3
White blood cell count increased subjects affected / exposed occurrences (all)	0 / 159 (0.00%) 0	0 / 164 (0.00%) 0	1 / 159 (0.63%) 1
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	0 / 159 (0.00%) 0	0 / 164 (0.00%) 0	3 / 159 (1.89%) 3
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 159 (0.00%) 0	0 / 164 (0.00%) 0	1 / 159 (0.63%) 1
Nervous system disorders Headache			

subjects affected / exposed occurrences (all)	5 / 159 (3.14%) 8	0 / 164 (0.00%) 0	4 / 159 (2.52%) 4
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 159 (0.63%) 1	1 / 164 (0.61%) 1	0 / 159 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 July 2019	The amendment includes clarifications to verbalize more detailed guidance as per the current status quo.
21 April 2020	The amendment was introduced due to the COVID-19 pandemic and its impact on the national health systems and public restrictions. The sponsor amended the clinical trial protocol for the duration of this pandemic. The aim of this amendment was to introduce mitigation measures for the negative effects of the COVID-19 pandemic on this clinical trial to ensure safety and well-being of the patients and health care staff at the trial sites. This amendment implied an addendum to the patient information sheet and informed consent form.

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.

This trial was partially disrupted by the COVID-19 pandemic and the Russia/Ukraine conflict. Mitigation measures were implemented to minimize the impact on study data. Supportive analyses do not indicate any problems with the reliability of the data.

Notes: